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Atabrine in the Treatment of Cardiac Arrhythmias

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ATABRINE can be used as a substitute for quinidine to convert auricular fibrillation and other abnormal cardiac rhythms to a normal sinus mechanism (*1*).

Chemically unrelated compounds often possess similar pharmacologic actions. For example, the antimalarial activities of quinine and atabrine (quinacrine hydrochloride) are well known, but they are unrelated chemically.

Similarly quinidine, an optical isomer of quinine, and atabrine have many similar physiological actions: both inhibit cholinesterase from the electric organ of *Electrophorus electricus* (*2*), dilate coronary vessels in perfused rabbit hearts (*3*), inhibit vagus-stimulated gastric secretion (*4*), increase the refractory period and decrease the excitability of perfused rabbit (*5*) and frog hearts (*6*), and paralyze vagus-inhibitory fibers to the dog's heart (*1*) (*7*).

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Quinidine has been used for many years to restore auricular fibrillation and other cardiac arrhythmias to regular sinus rhythm. Its actions include lengthening the refractory period and decreasing the rate of conduction in the auricular muscle, decreasing the vagus inhibitory effect on the auricle, and depressing auriculoventricular conduction. These actions combine to abolish the "circus" movement, and allow the sino-auricular node to again assume the role of pacemaker (*8*) (*9*).

Experimentally in dogs atabrine has been shown to restore normal sinus rhythm in auricular fibrillation as effectively as quinidine (*10*). Atabrine was also effective in restoring normal sinus rhythm in supraventricular tachycardias (*1*) (*11*) (*12*).

The toxic actions of atabrine include liver intoxication (*13*), skin discoloration (*14*) (*15*), dermatitis (*16*) (*17*) (*18*), aplastic anemia (*17*), central nervous system damage (*19*) (*20*), psychoses (*15*) (*21*), and gastrointestinal disturbances (*22*). However, these adverse effects occur in only a small number of persons taking atabrine and are of short duration; the only prolonged disturbance is the dermatitis (*16*) (*18*). Electrocardiographic changes have occurred in only a few patients (*8*) (*23*). It has been suggested that intravenous atabrine was toxic to perfused rat's or rabbit's heart. However, such solutions are strongly acid (*p*H 4.9), and solutions of the same *p*H not containing atabrine produced the same effect (*24*). Furthermore, the small volume of fluid injected (10 cc.) when diluted by blood would scarcely alter the *p*H of the blood.

Because of the possible toxic manifestations from prolonged use of atabrine, we limited the dosage of atabrine to a maximum of three separate intramuscular (gluteal) injections of 0.4 gm. each, dissolved in 10 cc. of 1 percent novocain solution (or 0.2 gm. intravenously in 10 cc. of normal saline), given every 6 hours (*1*) (*11*) (*12*). (Atabrine dihydrochloride is available in 0.2 gm. ampules.) With such methods relatively rapid high blood levels of atabrine are obtained. If normal sinus rhythm was restored prior to the second or third doses, the latter were omitted.

The following groups of patients were considered suitable candidates for atabrine therapy: (*a*) those with auricular fibrillation established less than 1 month regardless of associated valvular or nonvalvular heart disease; (*b*) those with "established" auricular fibrillation in whom some indication for conversion to a sinus rhythm, such as embolism or chronic failure, existed; (*c*) auricular flutter; (*d*) paroxysmal tachycardias; and (*e*) ectopic rhythms associated with recent hyocardial infarctions.

Since congestive failure is sometimes responsible for the perpetuation of auricular fibrillation (the E factor of Nahum and Hoff (*25*)),

it was our plan to treat and overcome congestive heart failure before giving atabrine.

If three doses of parenteral atabrine failed it was our intention to use oral quinidine in the accepted manner. Atabrine is excreted slowly, requiring 2 to 3 weeks after its administration is discontinued; therefore, we did not consider using oral atabrine because of the possible cumulative toxic effects (*21*) (*26*). Quinidine is excreted rapidly.

Auricular fibrillation is converted to normal sinus rhythm, with the use of quinidine, in about 60 percent of the patients (*27*) and with atabrine in about 50 percent (*1*). In previous reports where treatment with quinidine failed to restore normal sinus rhythm, atabrine was also unsuccessful. However, in these reports instances of auricular fibrillation associated with hyperthyroidism in which restoration of normal rhythm would not be expected without surgical intervention were included (*1*) (*11*) (*12*).

CASE REPORTS

Case 1.—A 36-year-old man with known rheumatic mitral valvular disease was admitted on 24 March 1949 because of dyspnea and vague joint pains. The physical findings were typical of mitral stenosis. Salicylates and bed rest were employed empirically although there was no evidence of rheumatic fever. After 3 weeks he was digitalized because of persistent dyspnea but his symptoms did not abate. One week later, while on maintenance doses of digitalis, he had auricular fibrillation. Three doses of atabrine (0.4 gm. each) were given intramuscularly 6 hours apart without effect. The following day quinidine (6 gr.) was given every 4 hours for 4 doses at which time the rhythm changed to a supraventricular tachycardia at a rate of 150. A few hours after this change he had chills and high fever which were assumed to be due to subacute bacterial endocarditis. Penicillin was given and the temperature became normal in 3 days. Attempts to stop the tachycardia by vagal stimulation were without effect. Quinidine, 6 gr. every 4 hours for 6 doses, was given without effect. Digitalis and quinidine were then discontinued, and 2 days later the rhythm changed to auricular fibrillation. Auricular fibrillation was still present 2½ months after onset, but, under sodium restriction, digitalis, and diuretics, compensation was maintained.

Case 2.—A 52-year-old man with known mitral stenosis and auricular fibrillation for 7 years had required maintenance doses of digitalis. In the past 2 years he had several episodes of decompensation. He was admitted on 11 April 1949 with symptoms compatible with splenic embolism. While under observation he had an attack of flank pain and transient hematuria interpreted to be due to a renal infarct and shortly thereafter he had a left hemiplegia. An attempt to restore normal rhythm with three doses of atabrine (0.4 gm. each) intramuscularly at 6-hour intervals failed. Six doses of quinidine, 6 gr. every 4 hours, were also given without altering the auricular fibrillation.

Case 3.—A 28-year old man was discharged from the Navy in 1945 because of an "enlarged heart." He was asymptomatic until August 1948 when he had auricular fibrillation. The rhythm was restored to normal with digitalization and quinidine, 6 gr. every 4 hours for 6 doses. Upon reducing the maintenance dose of quinidine from 3 gr. 3 times daily to 3 gr. once daily, he again had

auricular fibrillation. He was digitalized and quinidine was given as before. He remained asymptomatic for 8 months when he had a third paroxysm of fibrillation. He was readmitted on 29 April 1949 with auricular fibrillation and findings typical of mitral stenosis. There was no evidence of decompensation. He was given atabrine, 0.4 gm. intramuscularly at 6-hour intervals for 3 doses, without effect. Subsequently, he was digitalized and the rate slowed from about 120 per minute to about 100 but the arrhythmia persisted. After digitalization, atabrine, 0.4 gm., was given intramuscularly for 6 hours but without effect. Quinidine, 6 gr. every 4 hours, was then given orally. The rhythm changed to a sinus mechanism after the third dose of quinidine. Digitalis was discontinued and the patient was discharged. Maintenance doses of oral quinidine, 3 gr. 3 times daily, were prescribed.

Case 4.—This 37-year-old man was admitted on 9 September 1949 complaining of allergic skin reaction following the local application of a sulfonamide. He had had uncomplicated scarlet fever in childhood. In July 1949 he had a 3-day attack of "congestion of the lungs" and was then told that his heart rhythm was irregular.

Physical examination revealed a generalized bullous urticarial eruption over the entire body except for the face, hands, and feet. The heart was enlarged to the left. A murmur typical of mitral stenosis and an irregular rhythm characteristic of auricular fibrillation was heard. The apical rate was 102 and the radial rate was 88.

After appropriate therapy he was digitalized on 16 September 1949 with oral digitoxin and the following day he was given three doses of atabrine dihydrochloride, 0.4 gm., intramuscularly in 1 percent procaine at 6-hour intervals. The fibrillation remain unchanged. The next day quinidine sulfate, 3 gr. every 4 hours, was given. This dose was ultimately increased to 9 gr. every 4 hours without effect on the fibrillation.

Case 5.—A 54-year-old man was admitted on 15 March 1949 with right hemiplegia and aphasia. He had had hypertension for 3 years. At the time of admission the blood pressure was 145/100; the electrocardiogram showed left axis deviation with a "left ventricular strain pattern" and coronary insufficiency. On 16 April 1949 he was found to have a cardiac arrhythmia which, both clinically and by electrocardiogram, was auricular fibrillation. He was given atabrine, 0.4 gm. intramuscularly, at 6-hour intervals. The rhythm changed to a sinus mechanism 3 hours after the second dose. He was discharged; no further therapy was required.

Case 6.—A 60-year-old white man was admitted on 21 April 1949. He complained of substernal distress of several hours' duration. There was a long history of hospitalization because of cardiac disability. Examination revealed a blood pressure of 180/120 and a normal sinus rhythm. During examination he had generalized clonic convulsions, became cyanotic, and the pulse and blood pressure were imperceptible. An electrocardiogram (electrodes in place at the time of the convulsion) revealed first an auricular fibrillation and then a pattern interpreted as ventricular tachycardia. Atabrine, 0.2 gm. in 6 cc. of 1 percent procaine, was injected into the heart, followed in a few minutes by 10 cc. of 1 percent procaine. At the same time atabrine, 0.2 gm., was given intramuscularly. Within a few minutes the electrocardiogram pattern reverted to that of auricular fibrillation interrupted by runs of ventricular tachycardia, and the patient's general condition improved. Five hours later atabrine, 0.4 gm., was given intramuscularly and, about 3 hours later, the rhythm was noted to be

regular, confirmed by electrocardiogram. He remained in coma for 36 hours but made an uneventful recovery without any evidence of arrhythmia or signs of decompensation. Serial electrocardiograms failed to reveal any evidence of myocardial infarction. On 3 June 1949 he developed a fulminating bronchopneumonia and died within 48 hours. Autopsy showed no cardiac abnormality and no myocardial infarctions either fresh or old. The coronary arteries showed moderate arteriosclerosis but were not occluded.

Case 7.—A 79-year-old man was admitted on 23 April 1949 following pulmonary embolism secondary to phlebothrombosis. According to his physician an auricular flutter based on arteriosclerotic heart disease had been present since the attack. This did not respond to adequate digitalization and small doses of quinidine. On admission he manifested slow auricular flutter (auricular rate 180, ventricular rate 60). Atabrine, 0.4 gm. intramuscularly, was given five times, twice on the day of admission at 6-hour intervals and three times the following day, without influencing the rhythm in any perceptible manner. Subsequently all cardiac drugs were discontinued for 1 week following which he was redigitalized with digitoxin. The arrythmia was not changed. Six doses of quinidine, 6 gr. at 4-hour intervals, were then given and a sinus rhythm interrupted by occasional premature ventricular contractions occurred. The patient made a satisfactory recovery. Maintenance doses of digitoxin and quinidine were prescribed.

Case 8.—A 49-year-old white man was admitted on 11 May 1949 in mild shock with a diagnosis of massive anterior myocardial infarction. This was confirmed by electrocardiogram. During the third hospital day he lapsed into profound shock and had an absolute irregularity of the cardiac rhythm interpreted clinically as auricular fibrillation (electrocardiogram not obtained). In addition to blood transfusions and plasma, atabrine, 0.2 gm. in saline, was given intravenously. The rhythm became normal about 2 hours later and the blood pressure rose appreciably. About 8 hours after the restoration of normal rhythm the blood pressure again fell, and the rhythm was again irregular. Atabrine was administered intravenously as before but this time without effect. The patient died. At autopsy a recent massive anterior myocardial infarction was found.

Case 9.—A 53-year-old man was admitted on 27 June 1949 because of sudden onset of angina, weakness, faintness, and palpitation in the chest 6 hours previously. An electrocardiogram showed auricular fibrillation. Two doses of atabrine, 0.4 gm. in 10 cc. of 1 percent procaine, were given 6 hours apart without effect on the fibrillation. About 48 hours after admission (36 hours after atabrine) the rhythm spontaneously became normal. Subsequent electrocardiograms revealed changes suggestive of coronary insufficiency, but no infarction pattern appeared on serial tracings.

Case 10.—This 58-year-old man was admitted to the hospital on 11 August 1949 complaining of "high blood pressure" for 15 years, dyspnea and ankle edema for 8 months, and weakness of the left side for 1 month. He had been taking digitalis. There was no clear indication as to the time of onset of fibrillation.

Physical examination revealed a dyspneic man whose blood pressure was 250/140; pulse, 50; and apical rate, 72. The cardiac rhythm was irregular; the heart was enlarged to the left; and no murmurs were detected. There was a partial left hemiparesis. An electrocardiogram showed auricular fibrillation.

Digitalis and other medications including physical therapy were prescribed. The blood pressure remained 200/120.

Six weeks after admission he had several attacks of nocturnal paroxysmal dyspnea. After a satisfactory prothrombin level had been obtained with dicumarol, on 6 October 1949 he was given three intramuscular doses of atabrine, 0.4 gm. in 1 percent procaine at 6-hour intervals, without effect on his cardiac rhythm. The next day he was given quinidine sulfate, 3 gr. every 2 hours for eight doses, without effect on the fibrillation. Quinidine was then discontinued because of nausea.

His course after this was downhill and he died on 20 October 1949.

Case 11.—A 52-year-old white man was admitted on 12 September 1949 complaining of dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, and substernal pain radiating to the right of the sternum for 3 months, palpitation for 6 weeks, and ankle edema for 3 days. There had been no previous cardiac complaints.

The patient was a moderately obese and dyspneic white man with dullness and absent breath sounds at both bases of the lungs. The heart was enlarged 2 cm. to the left of the midclavicular line in the sixth intercostal space. There was an irregular rhythm with an apical rate of 110 and a pulse rate of 92. The blood pressure was 180/100. The liver was palpable 6 fingerbreadths below the right costal margin and was quite tender. There was a moderate edema of the ankles. He was treated by digitalization and maintenance doses of digitoxin, mercurial diuretics, ammonium chloride, and a salt-poor diet. By 21 September 1949 he no longer showed signs of failure but he still had auricular fibrillation. On that date he was given three doses of atabrine, 0.4 gm. intramuscularly in 1 percent procaine at 6-hour intervals. Twenty-four hours later his rhythm was still irregular. On 22 September 1949 quinidine sulfate, 3 gr. every 4 hours, was given. After 2 days, normal sinus rhythm occurred. He was discharged 1 week later. Maintenance doses of digitoxin and quinidine, 3 gr. three times daily, was prescribed.

Case 12.—A 2½-year-old girl had attacks of supraventricular tachycardia since the age of 7 months. There was no evidence of organic heart disease. Each episode was successfuly treated by digitalization. Atabrine, 0.1 gm. intramuscularly, was given twice, 4 hours apart, during the seventeenth and eighteenth attacks. Both times the pulse gradually slowed to normal during the 3 hours after the second injection. Review of the history shows that similar response was noted following digitalis therapy previously and that the attacks lasted from 12 to 24 hours no matter what therapy was employed.

A subsequent attack of tachycardia again become normal 1 hour after a second dose of atabrine, 0.1 gm., was given intramuscularly.

Case 13.—A 27-year-old woman was admitted on 1 May 1949 because of chest pain, dyspnea, and tachycardia. She was emotionally unstable and this had been apparent to previously consulted physicians. (Her husband had recently died of mitral stenosis (auricular fibrillation).) An electrocardiogram revealed a nodal tachycardia; rate 140. Atabrine, 0.3 gm. (patient's weight was 110 pounds) was given intramuscularly. The rhythm suddenly became normal 3½ hours later and her symptoms immediately subsided.

Case 14.—A 52-year-old man was admitted on 12 September 1949 complaining of dyspnea, orthopnea, nausea, desire to defecate, palpitation, and heartburn. All symptoms had appeared suddenly 2½ days previously. He had had no previous history of cardiac or gastrointestinal complaints. He had a tachycardia, rate 200, with the rhythm slightly irregular; the blood pressure was 150/90; but there were no signs of congestive failure. An electrocardiogram revealed

a nodal tachycardia, rate 180. That day he was given three injections of atabrine, 0.4 gm. in 1 percent procaine, intramuscularly, at 6-hour intervals. The rate slowed to 140. Two hours after the last dose of atabrine he was given 1.2 mg. of digitoxin by mouth and quinidine sulfate, 6 gr. every 4 hours. Eight hours later his rhythm became and remained normal. There was no evidence of myocardinal infarction, and the patient was discharged on 17 October 1949. Maintenance digitoxin and quinidine sulfate were prescribed.

Case 15.—A 65-year-old white man was admitted 25 October 1949 complaining of severe dyspnea of 2 days' duration. Previously he had had dyspnea on exertion for 2 years. He had no chest pain.

On physical examination the patient was orthopneic and cyanotic and the neck veins were distended. Bilateral râles and wheezes were heard at both lung bases; the heart was enlarged to the left of the midclavicular line; and the rhythm was rapid and regular at 180. The liver was tender and palpable 4 cm. from the right costal margin. There was no ankle edema.

An electrocardiogram revealed a supraventricular tachycardia, rate 180. Attention was first directed to the congestive failure. He was digitalized with intravenous cedilanid, given oxygen, morphine, and atropine every 4 hours, aminophylline intravenously and by mouth, and a "bloodless phlebotomy" by rotation of tourniquets. The next morning (26 October 1949) he had less dyspnea, the chest was clearer, but the tachycardia persisted (rate 178). That day he was given 4 doses of atabrine, 0.4 gm. intramuscularly every 6 hours. On 27 October 1949 the electrocardiogram showed a mixed auricular flutter-fibrillation. Quinidine, 3 gr. every 4 hours, was given and after 24 hours electrocardiogram showed a rate of 140 and a nodal tachycardia. The dose of quinidine was increased to 6 gr. every 4 hours and a day later, on 29 October 1949, the electrocardiogram showed auricular fibrillation.

After another 6 doses of quinidine, 6 gr. every 4 hours, the rhythm was found to be normal with a rate of 94. Since that time the rhythm has been regular. Maintenance doses of digitoxin and quinidine, 3 gr. 4 times daily, were continued.

COMMENT

Atabrine parenterally is of no more value than oral quinidine in restoring auricular fibrillation associated with mitral stenosis to normal rhythm in either acute or chronic cases. In one patient with acute fibrillation, quinidine was successful three times; whereas, atabrine on the one occasion it was used was of no avail.

In the arteriosclerotic and hypertensive group, in three patients with acute auricular fibrillation normal rhythm was restored by atabrine. One patient probably had ventricular fibrillation in addition. The result here is clouded by the fact that procaine was given intracardiacly and intravenously at the same time. In one patient in whom normal rhythm was restored by atabrine, death occurred 8 hours later from resumption of fibrillation. This might have been prevented by administering oral quinidine after normal rhythm was established.

No patient with hypertensive and arteriosclerotic heart disease with chronic arrhythmias was benefited by the use of atabrine. However, the patients with auricular flutter and auricular fibrillation were converted by quinidine. From this small series it appears that atabrine is not as efficacious as quinidine.

In auricular fibrillation associated with nonvalvular heart disease, especially that of short duration, normal rhythm was restored in five out of seven patients (71.4 percent) while in fibrillation associated with valvular disease normal rhythm occurred in one out of four (25 percent).

Atabrine or quinidine restored normal rhythm in all four patients with tachycardia. Two of these were of the type (supraventricular) in which normal rhythm may return spontaneously. In two patients the accompanying coronary arteriosclerosis was evidenced by signs of congestive failure. Atabrine failed to restore normal sinus rhythm, but after administering quinidine for from 48 to 72 hours normal rhythm occurred. In our series of 15 cases normal phythm was restored with atabrine in 5, with quinidine in 5, and 5 were failures, giving a total conversion rate of 66 percent. In previous reports (*1*) (*27*) normal rhythm was restored in 60 percent with quinidine and in 50 percent with atabrine. It is realized that the number of cases is statistically too small to draw significant conclusions. However, the results suggest that with the use of both drugs in the future, perhaps a slightly higher percentage of cases might be converted.

If the patients with tachycardia are excluded from the results it may be seen that in 54.6 percent of patients with auricular fibrillation, including one of auricular flutter, normal rhythm is restored by the use of either atabrine or quinidine. This figure compares favorably with those previously reported (*1*) (*27*).

SUMMARY

Atabrine's value appears to lie in the treatment of auricular fibrillation of short duration associated with nonvalvular heart disease. It was of no more value than quinidine in patients with chronic fibrillation either with or without valvular disease and is of questionable value in the treatment of supraventricular tachycardia.

In our series restoration of normal rhythm with the use of atabrine or quinidine was successful in 66 percent of patients with arrythmias.

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SONIC VIBRATED LEPTOSPIRAE AS ANTIGENS IN THE COMPLEMENT FIXATION TEST FOR THE DIAGNOSIS OF LEPTOSPIROSIS, by Raymond Randall, *Colonel, VC, U. S. A.;* Psyche W. Wetmore; and Albert R. Warner, Jr. Journal of Laboratory and Clinical Medicine **34**: 1411–1415, Oct. 1949.

Because a simple and reliable diagnostic test for leptospirosis was not available, a study was undertaken to develop an antigen for use in a complement-fixation test that could be performed in any laboratory conducting the Wassermann or similar complement-fixation tests. Since antigens prepared by the usual methods gave unsatisfactory results, experiments were undertaken to produce a suitable antigen; and it was found that leptospirae ruptured by sonic vibration yielded an antigen of considerable specificity and sensitivity. Serums from patients with leptospirosis caused by *Leptospira icterohaemorrhagiae* and *Lept. grippotyphosa* reacted with *Lept. canicola* and *Lept. icterohaemorrhagiae* antigens to titers regarded as specific for leptospirosis.—*Abstract.*

Assay of Gonadotropins in the Diagnosis of Neoplasms

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DETERMINATION of the excretion of gonadotropins in the urine is of value in diagnosing neoplasms arising from the testes and the chorionic villi. Normally, the anterior lobe of the pituitary stimulates the ovaries and testes by means of specific gonadotropins that are believed to be secreted by the basophilic cells of this gland. One of these substances is known as follicle stimulating hormone (FSH) or prolan A. This substance, in women, stimulates the growth and maturation of ovarian follicles, and in the presence of a small amount of luteinizing hormone results in estrogen production and ovulation. In men this hormone stimulates the cells of the seminiferous tubules and produces spermatogenesis. Another gonadotropin which is secreted by the pituitary is the interstitial cell stimulating hormone, luteinizing hormone, or prolan B. This substance stimulates the interstitial cells of the ovary in some animals and in human beings stimulates the granulosa cells to undergo luteinization and form the corpus luteum after they have been under the influence of FSH. In male animals it stimulates the interstitial cells of Leydig to produce the male sex hormone. This hormone can also stimulate the seminiferous tubules indirectly, since it stimulates the Leydig cells, which, in turn, release testosterone. This, at least in small doses, seems to promote spermatogenesis. A third hormone of the pituitary, the lactogenic hormone, is capable of inducing and maintaining lactation in the breasts of animals with intact pituitary glands. It also prolongs the life of the corpus luteum. The chorionic trophoblastic cells of the human placenta also produce a gonadotropin. It has a luteinizing action, and, consequently, is frequently referred to as "anterior pituitarylike hormone." Normally, in pregnant animals, its function seems to be stimulation of the luteal cells in order that they keep functioning until the placental tissue starts the formation and secretion of progesterone. In contrast to the pituitary luteinizing hormone, however, it possesses no important stimulating action on the

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ovaries in human beings other than prolongation of the presence of the corpus luteum. In male animals it brings about testicular descent in cryptorchism and is capable of stimulating the interstitial tissue with a resultant outpouring of androgens. Equine gonadotropin is produced by the placenta of the pregnant mare and is present in the blood of this animal during pregnancy. It is unique in that it is not excreted in the urine of the pregnant mare and also in that it has both follicle-stimulating and luteinizing properties.

All of these substances are complex glycoproteins that vary in their isoelectric points, in their molecular weights, and in the composition of the active carbohydrate and amino nitrogen groups. All are soluble in water and may be precipitated by alcohol, benzoic acid, or tannic acid, a property that allows their concentration and partial purification in the quantitative Aschheim-Zondek test. Their potency is lost slowly on standing in solution, and is destroyed readily by heating, or by excess acid or base.

The tests for gonadotropins in urine or blood can be divided into qualitative tests for the diagnosis of pregnancy, and quantitative tests that determine the excretion of gonadotropins in the urine in 24 hours. The pregnancy tests vary not only with the animals used, but also with the time required to carry out the determination. In the Aschheim-Zondek test, immature female mice or rats are usually used. While 96 hours are needed for the completion of this test, only 48 hours are needed for the Friedman test, which uses mature female rabbits that have been isolated for 3 weeks. Several pregnancy tests requiring less than 24 hours for their completion are available. One such test depends on the hyperemia of the ovaries produced in the immature rat by the injection of urine containing chorionic gonadotropin; the optimum time for reading the reaction varies from 2 to 24 hours according to various investigators. Another group of rapid pregnancy tests uses various species of frogs and toads. The South African clawed toad (*Xenopus laevis*) reacts to the injection of urine from a pregnant woman by the extrusion of grossly visible ova, usually within 24 hours, while the male South American toad (*Bufo arenarum*) and the male North American frog (*Rana pipiens*) react to chorionic gonadotropin by the release of spermatozoa, usually within 2 hours. These can be easily seen by microscopic examination of the cloacal fluid.

The only test which has been consistently used for quantitative assay of gonadotropins is the quantitative Aschheim-Zondek test. The Fourth Army Medical Laboratory uses the quantitative Aschheim-Zondek test as modified by Cutler and Owen (*1*) and by Vermooten and Hettler (*2*). The gonadotropins are concentrated by precipitation from aliquots of a 24-hour specimen of urine by adding 5 vol-

umes of 95 percent ethyl alcohol and allowing the mixture to stand overnight at 4° C. The precipitated glycoproteins are next washed with ether, dried, and put into solution by dissolving them in 8 cc. of distilled water, giving either a fivefold or tenfold concentrate, depending on whether 40 cc. or 80 cc. of urine was used. The concentrate is injected subcutaneously into immature female mice, weighing 8 to 10 gm., in 5 doses, 2 on the first day, 2 on the second day, and 1 on the third day. One mouse is given a total of 0.5 cc. of the fivefold concentrate which equals 2.5 cc. of urine while others receive an equivalent of 5, 10, and 20 cc. of urine. The last is injected with the tenfold concentrate. The mice are killed with chloroform 48 hours after the last injection and are examined for enlargement of the uterus and/or formation of either hemorrhagic follicles or corpora lutea.

The mouse unit (M. U.) with which the gonadotropins are measured equals the smallest dose of urine expressed in milliliters that produces unmistakable enlargement, usually with hyperemia of the bifurcated uterus, and/or hemorrhagic follicle or corpus luteum formation. One thousand divided by this unit equals the M. U. per liter. Since it takes about five times as much gonadotropin to cause ovulation as it does to induce secondary estrus with enlargement of the uterus and opening of the vaginal orifice, the mouse units giving an enlarged uterus are multiplied by five if the ovaries show either corpora hemorrhagica or corpora lutea (*2*). The amount of the gonadotropins needed to form corpora hemorrhagica or corpora lutea is influenced by the ratio of FSH and chorionic gonadotropin present in the urine as well as possible activity of the test animal's pituitary. Nevertheless it has been the experience of the writer that the fivefold relationship is usually present. The technique and reading of the quantitative tests are summarized in table 1. The 50 and 100 M. U. assays are run in duplicate since these mice receive the more concentrated solutions, and consequently are more prone to die. If all of the mice tested show positive findings, the assay can be carried even farther by the use of undiluted and diluted urine (table 2).

TABLE 1

Test mouse	Schedule of injections					Total dose in milliliters	Equivalent quantity of urine in milliliters	M. U./L required to produce positive	
	A. M.	P. M.	A. M.	P. M.	A. M.			Uterine findings	Ovarian findings
1	0.1	0.1	0.1	0.1	0.1	0.5	2.5	400	2,000
2	.2	.2	.2	.2	.2	1.0	5.0	200	1,000
3	.4	.4	.4	.4	.4	2.0	10.0	100	500
4	.4	.4	.4	.4	.4	2.0	10.0	100	500
5	.4	.4	.4	.4	.4	2.0	20.0	50	250
6	.4	.4	.4	.4	.4	2.0	20.0	50	250

TABLE 2

Test mouse	Total amount of urine given in 5 injections	M. U./L required to produce positive	
		Uterine findings	Ovarian findings
1	2 ml. of undiluted urine	500	2,500
2	1 ml. of undiluted urine	1,000	5,000
3	2 ml. of urine diluted 1/10	5,000	25,000
4	1 ml. of urine diluted 1/10	10,000	50,000
5	2 ml. of urine diluted 1/100	50,000	250,000
6	1 ml. of urine diluted 1/100	100,000	500,000

The amount of the gonadotropin excreted in the urine of normal persons is important if this assay is to be used for diagnostic purposes. Gonadotropins do not appear in the urine until about a year before the onset of menstruation in girls, and in boys a positive response cannot be obtained before the age of 12 or 13 years (*3*). The normal values obtained in adults vary somewhat with different methods of concentration of gonadotropins in the quantitative Aschheim-Zondek test and also the endpoints used. The levels presented here are those obtained by this laboratory and other laboratories using similar techniques (*4*) (*5*) (*6*), and refer to gonadotropins arising from the pituitary gland.

The normal menstruating woman excretes up to 100 M. U. in 24 hours usually with a peak of excretion near the middle of the cycle which is probably related to ovulation, while the castrated or postmenopausal women will excrete up to 500 M. U. of gonadotropins in 24 hours. Here the pituitary gland attempts to stimulate an organ that is either no longer present or nonfunctional, thereby increasing the amount of FSH formed for a period varying from 6 months to 30 years (*3*). On the other hand, the normal man excretes less than 50 M. U. in 24 hours. In some hypogonadic or castrated men the excretion is slightly elevated, but never as high or as constant as in postmenopausal women.

The group of neoplasms with which quantitative studies of gonadotropin are most frequently used as an aid in diagnosis in the Army, are the testicular tumors (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, and chorio-epithelioma). This group of tumors according to Friedman and Moore (*7*) probably arises from embryonic germ cells, with the seminoma coming from primordial germ cells and being composed of mononuclear growths. On the other hand, teratoid tumors and embryonal carcinomas which, according to these workers, include the chorio-epitheliomas, probably arise from more primitive embryonic germ cells which have the capacity to form both somatic and trophoblastic tissue. Occasionally seminomas will metastasize with formation of trophoblastic tissue, indicating that there must be primitive embryonic cells present in these tumors at times. Patients

with testicular tumors may excrete an abnormal amount of the gonadotropins in the urine and their urine will occasionally give a positive test for pregnancy. Ferguson (*8*) attempted to correlate the type of neoplasm found with the amount of the gonadotropins formed and proposed a classification of these tumors which was based on the amount of the gonadotropins in the urine. He believed that the larger the amount of this hormone excreted, the more embryonal the tumor as well as the larger the mass of viable tissue present. Ferguson also believed that the embryonal tumor, as it grew, produced an unidentified substance or hormone which stimulated the anterior lobe of the pituitary to secrete an increase of FSH.

It appears, however, that the pituitary gland does not enter into this process, but that the embryonic tumor itself forms the gonadotropins since the tumor tissue can be shown to have a high concentration of the active material if there is excretion of these substances before removal of the neoplasm (*9*). The presence of abnormal amounts of gonadotropins in the urine is not related so much to the structure of the tumor as to whether there is chorionic tissue present either in the primary tumor or in the metastases. Furthermore, Ferguson's belief that the quantitative test is a reliable means of differentiating types of testicular tumors is no longer accepted. Cahill (*10*) stated that the amount of the gonadotropins present with these tumors is an index of the amount and activity of syncytial secreting cells (presumably syncytiotrophoblasts). On the other hand, Stewart and his coworkers (*11*) reported that tissue cultures of placental tissue show a direct correlation between the growth of cytotrophoblasts and the production of gonadotropins. They were unable, however, to grow the syncytial cells well enough so that they could determine which, if any hormones, were elaborated by these cells. Further evidence that the cytotrophoblast is instrumental in the elaboration of gonadotropin, is the observation that at about the middle of pregnancy, when normally the excretion of gonadotropins is decreasing, the layer of cytotrophoblasts disappears in the placental villi (*12*). Whether it is only one or both of these cells which secrete gonadotropin is not clear.

Although focal chorio-epitheliomas are rarely observed in seminomas, about 4 percent of the 922 tumors studied by Friedman and Moore (*7*) contained both seminomatous and embryonal carcinomatous tissue. Even though the tumor is primarily a seminoma, the metastases may be embryonal carcinoma with active secretion of gonadotropin. An example is the following case.

CASE REPORT

A 33-year-old man first noted a hard painless nodule on one testis in March 1947. An assay of urinary gonadotropins revealed less than 100 M. U. per

liter of urine at this time but 1 month later revealed 200 M. U. per liter. Several examinations revealed 100 M. U. per liter. A unilateral orchidectomy was performed and the pathologic diagnosis was seminoma without extension into the cord vessels. About 2 months later, 2,000 M. U. of gonadotropin per liter of urine was found, and high voltage roentgen therapy was started. In November, an intravenous pyelogram revealed a deviation of one ureter, which was thought to be caused by a retroperitoneal mass. The excretion of gonadotropins at this time varied from 2,000 to 5,000 M. U. per liter. A retroperitoneal lymph node was resected and the microscopic examination revealed an undifferentiated carcinoma.

The patient died after a rather long and stormy illness. An assay of gonadotropins several months before death showed more than 16,000 M. U. excreted in the urine in 24 hours. Unfortunately, the exact level was never determined.

The autopsy showed multiple visceral and pulmonary metastases while the microscopic examination showed this to be an embryonal carcinoma with some of the characteristics of a seminoma.

In contrast a 26-year-old soldier whose primary tumor was an embryonal carcinoma had widespread metastases before death and only embryonal carcinoma was found. The highest titer of gonadotropins obtained in this case was 150 M. U. in 24 hours.

Friedman and Moore (*7*) stated that in their series of 922 testicular tumors some embryonal carcinomas had a striking morphologic resemblance to the cytotrophoblastic cells of chorio-epitheliomas. This may explain the elaboration of gonadotropins by tumors that are considered embryonal carcinomas and not chorio-epitheliomas. It is possible that these cells are so anaplastic that they have lost their power to elaborate this hormone. Another factor which is not always appreciated is that in any pathologic examination only a few blocks of tissue are taken from a tumor or its metastases for study, and chorionic tissue may not be present in the blocks chosen (*13*).

The hormone produced by the malignant tissue is chorionic in type (*14*) (*15*). The fact that about 12 percent of these malignant tumors arise in undescended testes may be confusing and many of these patients probably represent hypogonadal states in which the pituitary is attempting to stimulate these organs by an increase in the FSH produced (*15*) (*16*). Either unilateral castration or destruction of a testis by the tumor may decrease the amount of androgens secreted in the body with a resultant increase, usually slight in the amount of the gonadotropins in the 24-hour urine specimen (*2*). This is caused by an increase in the FSH elaborated by the pituitary. Postoperative high voltage roentgen therapy to the genital area may be the factor in this castration effect, but the roentgen rays primarily affect the seminiferous tubules and have relatively little effect on the Leydig cells which secrete the androgens (*17*). The differentiation of pituitary gonadotropin (FSH) and chorionic gonadotropin involves the use of either hypophysectomized female rats which give only luteinization of thecal cells when stimulated with chorionic gonadotropin or the destruction

of the FSH by extraction of the chorionic gonadotropin with tricresol. Careful examination of the amount of the gonadotropins needed to increase the weight of the ovaries of infantile rats may also be used since small amounts of FSH will give a maximum weight increase rapidly in contrast to the slower action of large doses of chorionic gonadotropin (*15*). One can readily see that the differentiation of these two hormones in the ordinary laboratory is impractical.

The fact that there is abnormal excretion of gonadotropins as assayed by the usual methods in a patient with a testicular tumor is of little use in determining whether metastases have occurred preoperatively. If, however, a high value is obtained, one can usually assume that trophoblastic tissue is present. After the primary tumor has been removed, persistent high abnormal excretion of gonadotropins or a rise after an initial fall in titer is evidence that secretory metastatic cells are present elsewhere in the body. Usually quantitative assays of gonadotropins are determined postoperatively every month for at least 3 months with a gradual lengthening of the intervals for the next 3 to 5 years.

The assay of excreted gonadotropins is also of aid in the diagnosis of both hydatid moles and chorio-epitheliomas in women. Both are derived from chorionic tissue and, as such, they elaborate varying amounts of the gonadotropins. Normally, about 4 weeks after conception the amount of the gonadotropins in the urine increases and steadily rises to a peak between the sixth and twelfth weeks of gestation. The excretion of gonadotropins then drops rapidly to a much lower level during the remainder of pregnancy. After the delivery of the placenta, the level of gonadotropins falls rapidly, and within a week usually reach levels observed in nonpregnant women. Whereas, in a normal pregnancy the peak of excretion of gonadotropins is reached in the first trimester, in hydatid degeneration of the placenta, there is usually a larger excretion of gonadotropins in the third to fifth month of pregnancy (i. e. from 200,000 to several million M. U. in 24 hours) when normally the titer of gonadotropins is decreasing (*18*). The excretion of gonadotropins appears to be roughly proportional to the amount of trophoblastic tissue present. By means of tissue culture, Jones, Gey, and Gey (*19*) showed that tissue from both ectopic pregnancies and hydatidiform moles produces gonadotropins for periods of 2 to 6 months. In general, if a malignant chorio-epithelioma occurs, the excretion of gonadotropins is even higher than in a patient with a hydatid mole. Significance is placed on the detection of gonadotropins in the spinal fluid in patients with hydatid mole and chorio-epithelioma, which is said never to occur in a normal pregnancy (*18*). Several cases of normal pregnancy have been recorded in which it was possible to obtain a positive Aschheim-Zondek test (*20*). Hydatidiform moles and chorio-epi-

theliomas have also been known, on rare occasions, to elaborate virtually no gonadotropins (*21*). The excretion of gonadotropin is not only influenced by the amount of chorionic tissue present but also by its proximity to blood supply and the capacity of the cells present to elaborate this hormone. It may be that the absence of this capacity is an index of the degree of anaplasia of the tumor cells. Novak stated that both cytotrophoblasts and syncytial trophoblasts participate in the malignant process of a chorio-epithelioma, but that it is commonly believed that tumors showing a predominance of syncytial elements are less malignant than those in which the cytotrophoblasts predominate (*12*).

The usual procedure after the passage of a hydatid mole, is to obtain periodic 24-hour quantitative assays of gonadotropins in order to detect either residual chorionic tissue or the development of a chorioepithelioma. Levels of detectable gonadotropin may, however, persist for 4 to 12 weeks after successful passage of a hydatid mole, since the time required for these levels to disappear depends on the original height of the blood level and the rate of excretion.

Each patient who has passed a hydatid mole should be followed by quantitative studies of gonadotropins every 2 to 4 weeks for the first 6 months, every 2 or 3 months in the second 6 months, and at least twice a year thereafter for several years. Since a single determination is of limited value, it is important to determine whether the hormone is increasing or decreasing. No matter how long after removal of the tumor, falling levels can only mean that no new hormone has been produced and that there is no functioning chorionic tissue left. Any rise in level indicates either recurrence of the tumor, the development of malignancy, or another pregnancy.

Since gonadotropins are produced by the basophilic cells of the pituitary in the normal person, one would expect excessive amounts of these hormones in cases of pituitary basophilic tumors which may be the cause for some cases of Cushing's syndrome. This occurs only sporadically, if at all, and relatively early in the course of the disease (*3*). Consequently, the value of the assay for these substances is practically nil in this pathologic entity.

CONCLUSIONS

The quantitative determination of the excretion of gonadotropins in the urine is of aid in the diagnosis of neoplasms arising from the testes and from the chorionic villi. Because of the variation encountered, this assay should be used only as confirmatory evidence in the diagnosis of these neoplasms and should not be regarded as a necessary diagnostic criterion. The quantitative assay of gonadotropins is also of aid in the detection of metastases or recurrence of these tumors.

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An Evaluation of the Treatment of Chronic Osteomyelitis

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SEVENTY-TWO cases of chronic osteomyelitis observed and treated over a period of 20 months are presented in order to compare the results of several methods of treatment. The average age of the patients in this series was 25, the youngest was 19 and the oldest was 36. In 90 percent, the etiologic factors were either gunshot wounds or compound fractures from other causes, 5 cases followed open reduction, and in 3 the lesion was hematogenous. Bacteriostatic agents including penicillin, streptomycin, and the sulfonamides were used systemically in each case according to the indication determined by the type of organism and its sensitivity and resistance. None was used locally in conjunction with any of the surgical procedures. The most common organism recovered from the wounds was hemolytic *Staphylococcus aureus* (61 percent). Others included *Proteus*, *Staph. albus*, *Staph. aureus*, and *Bacterium coli*, in that order. The average period of drainage, preoperatively, was 12 months.

SURGICAL TREATMENT

The incidence of bone involvement in 72 cases was as follows: tibia, 30 (42 percent); femur, 16 (22 percent); humerus, 8 (11 percent); ulna, 4 (6 percent); elbow, 3 (4 percent); radius, 2 (3 percent); pelvis, 2 (3 percent); finger, 2 (3 percent); ankle, 2 (3 percent); scapula, 1 (1 percent); os calcis, 1 (1 percent); and hip, 1 (1 percent).

The various operative procedures employed, together with the results in terms of postoperative drainage, are shown in table 1. The average period of drainage postoperatively for the entire series was 2 months. In 35 cases, or 49 percent, there was no drainage. In the remaining 37, or 51 percent, drainage persisted for an average of 3½ months.

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TABLE 1

Type of operation	Number of cases	Percent of series	Number of cases with no postoperative drainage	Percent with no postoperative drainage
Sequestrectomy	36	50	13	39
Saucerization	17	24	9	53
Saucerization plus muscle pedicle flap	7	10	6	86
Sinusectomy	5	7	4	80
Saucerization plus iliac chips	3	4	0	0
Sequestrectomy and epithelialization	2	3	1	50
Amputation	1	1	1	100
Resection of tibia	1	1	1	100
Total	72	100	35	

For purposes of comparison, the number of amputations and resections of the tibia, as well as the sequestrectomies and epithelialization, should not be included as they are too small in number to be of any significance. The latter cases consisted simply of the application of either split thickness or pinch grafts to the granulating areas within the depths of the wounds. In the small number treated by implantation of iliac bone chips in the manner described by Prigge (*2*), results were uniformly poor. However, in the cases treated by filling the defect with a muscle pedicle flap, a procedure referred to by Starr (*4*) as early as 1922, and described by Mercer (*1*) in 1933, the results were good enough to warrant further comment and more detailed analysis. It will be noted that the highest percentage of cases which remained closed (86 percent), fell in this group. This is essentially the same as the figure reported in a larger series by Stark (*3*) (84 percent).

Of the 7 cases treated by this method, 6 involved the femur, and in none of these was there any drainage postoperatively. The average period of preoperative drainage had been 13½ months. The remaining case involved the humerus, and in this case drainage persisted for 1 month postoperatively.

In order to provide a basis of comparison of methods of treatment and results obtained on specific bones, the following analyses of treatment of the femur and the humerus are presented. In 16 cases of osteomyelitis of the femur, the following operations were done: Muscle pedicle flap in 6 cases—no postoperative drainage; sequestrectomy in 5 cases—no postoperative drainage in 40 percent, the average period of postoperative drainage was 2 months; saucerization in 4 cases—no postoperative drainage in 50 percent, the average period of postoperative drainage was 3 months; and sinusectomy in 1 case—no postoperative drainage.

In 8 cases of osteomyelitis of the humerus the following operations were done: Sequestrectomy in 4 cases—no postoperative drainage in 25 percent, the average period of postoperative drainage was 1

month; saucerization in 3 cases—no postoperative drainage in 33 percent, the average period of postoperative drainage was 2 months; and muscle pedicle flap in 1 case with postoperative drainage for 1 month.

CASE REPORTS

Sequestrectomy.—S. M. C., a 19-year-old man, was admitted on 22 September 1946 with a history of pain and swelling of the left knee of 3 months' duration. One week following admission the patient sustained a fracture of the left femur. Roentgenograms showed rarefaction and a moth-eaten appearance of the bone (fig. 1). The leg was placed in traction and later in a hip spica. On 13 January 1947, check films showed the formation of a sequestrum at the fracture site (fig. 2). Two months later a sinus developed, and on 7 March 1947, a sequestrectomy was performed with primary closure. Seven months later, there was no evidence of infection or drainage (fig. 3).

Figure 1.—Pathological fracture, perostitis, and osteomyelitis areas (18 November 1946).

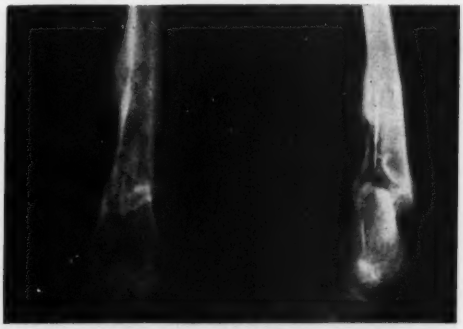

Figure 2.—Sequestrum of fracture site (5 March 1947).

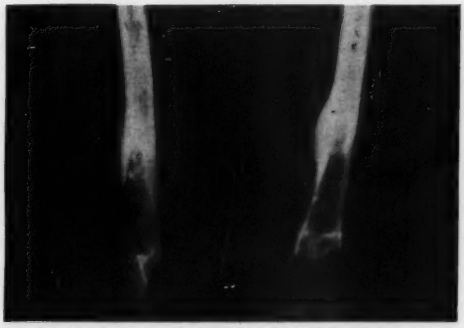

Figure 3.—Four months after operation (15 July 1947).

Saucerization.—L. J. R., a 23-year-old white man, had an acute hematogenous osteomyelitis followed by drainage from the right hip on 21 December 1945. He was transferred to this hospital on 24 March 1946 with the leg in a hip spica. After removal of the cast the leg continued to drain in spite of massive doses of penicillin and local

Figure 4.—Osteomyelitis of head of femur and sequestrum in acetabulum (18 July 1946).

Figure 5.—One year later, 8 months postoperatively, showing healing and beginning fusion.

irrigations with tyrothricin (fig. 4). On 7 November 1946, the acetabulum was saucerized, with removal of almost the entire iliac portion. The femoral head was denuded and a hip fusion was performed. The drainage ceased. However, on 28 December 1946, two sinuses appeared over the right buttock, and the cast was removed. Cultures revealed *Bacillus proteus*. The patient was given streptomycin, but no alteration in drainage occurred. On 4 March 1947, a sinusectomy of the right buttock was performed and numerous connecting sinuses were found in the fascial and muscle planes. These were completely resected and the incision closed primarily. No drainage occurred susequently (fig. 5). On 15 September 1947 roentgenograms showed complete fusion of the right hip.

Figure 6.—Anteroposterior view showing sequestrum and necrotic areas (29 July 1946).

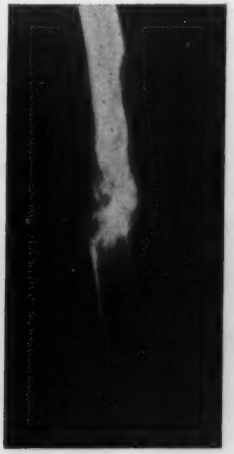

Figure 7.—Lateral view before operation.

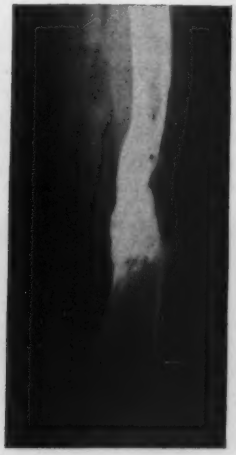

Figure 8.—Postoperative roentgenogram.

Figure 9.—Preoperative film, showing sinus injected with lipiodol.

Saucerization and muscle pedicle flap.—W. S. B., a 26-year-old white man, sustained a compound gunshot fracture of the left femur on 6 June 1945. The leg had been immobilized in a cast and the patient was transferred to this activity (figs. 6 and 7). On 19 September 1946 the fracture was well healed, but drainage persisted. At this time a saucerization and muscle pedicle flap operation was performed on the left femur. The incision healed primarily, but 1 month following surgery a small sinus appeared, from which a suture was removed. The sinus healed primarily within 10 days and the patient was discharged from the hospital 6 months later, with no drainage and a full range of motion of the left knee and hip (fig. 8).

Sinusectomy.—N. L. H., a 34-year-old white man in October 1944 sustained a compound gunshot fracture of the neck of the left femur. Saucerization was performed in May 1945. The wound apparently healed, but every 1 to 2 months abscess formation and drainage occurred. On 19 September 1946, a sinusectomy was performed and closed tightly and primary healing occurred (fig. 3). Five months later the patient was discharged to duty. He had had no recurrence.

Saucerization and iliac graft.—I. T. S., a 30-year-old white man, sustained a compound gunshot (mortar) fracture of the upper third of the right tibia with loss of bone substance. A mixed pyocyaneous infection followed. On admission to this hospital, 5 months later, the tibia had healed except for a bony defect of the anterior portion of the upper tibia which discharged foul, purulent material. Cultures revealed nonhemolytic staphylococcus and pyocyanase. Seven months after admission, saucerization and sequestrectomy was performed. The wound continued to drain profusely, clearing up after 10 months of local therapy with penicillin and tyrothricin. The cavity remained and a moderate discharge persisted (fig. 10). On 24 September 1946, a second sauceriza-

Figure 10.—Large cavity, prior to filling with iliac chips (16 August 1946).

Figure 11.—Four weeks after placing of iliac chips (15 November 1946).

tion and sequestrectomy was performed, followed by multiple iliac chip grafts on 17 October 1946. On 2 November 1946 the entire area became infected. A culture at this time revealed hemolytic streptococcus, gram-negative rods and *B. subtilus*. The wound was irrigated with acetic acid and tyrothricin alternately, without result (fig. 11). On 23 November 1946 the wound was completely cleaned out, and no viable bone chips were found. The patient was later discharged from the hospital although the wound was still draining.

Amputation.—F. L. V., a 25-year-old white man sustained bilateral compound trochanteric gunshot fractures of the femurs on 29 July 1945. The patient

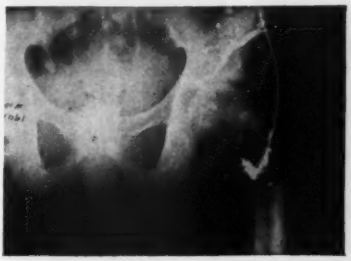

Figure 12.—Preoperative film (reversed in printing), showing massive infection of neck and upper shaft of right femur.

Figure 13.—Three months after disarticulation of right hip.

was admitted to this hospital on 20 June 1946 in a hip spica with multiple decubitus ulcers and a foul, purulent discharge from the wound in the right thigh. He had an ununited, comminuted, trochanteric fracture of the right femur; the left femur had united. Cultures at this time revealed gram-negative rods and streptococci. He also had bilateral urinary calculi and a pyelitis which was resistant to local treatment (fig. 12). On 6 January 1947 a disarticulation of the femur was performed and the stump allowed to granulate (fig. 13). Seven months later the patient was discharged from the hospital, free from wound drainage and urinary complications. He had gained 30 pounds in weight.

Resection of middle third of tibia.—R. L. C., a 22-year-old white man, sustained a compound, comminuted fracture of the tibia on 23 May 1946. Three days later an open reduction and débridement, and immobilization of the fracture with a Lane plate, was done. Osteomyelitis occurred and the patient was transferred to this activity on 3 November 1946. The plate was removed on 13 December 1946, but the infection continued. On 28 February 1947, roentgenogram showed the middle third of the tibia to be sequestrating (fig. 14). On 4 March 1947 approximately 8 inches of the tibia was removed by block resection. The wound was closed tightly and it healed primarily (fig. 15). On 11 August 1947 the defect was replaced with a combined fibular and iliac graft (fig. 16). At the present time, approximately 3 months later, there has been no drainage.

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Figure 14.—Massive sequestration of large tibial fragment, immediately before operation.

Figure 15.—Three months after block resection.

Figure 16.—Split fibular intramedullary and onlay grafts in place (on right); opposite leg from which graft was removed (on left).

SUMMARY

Seventy-two cases of chronic osteomyelitis have been reviewed in an attempt to demonstrate the relative value of several forms of surgical treatment.

Although the number of cases included in the several categories is not large, it is concluded that the use of the muscle pedicle flap, which produced excellent results in 86 percent in this series, is the method of choice in the treatment of chronic osteomyelitis.

The use of iliac chips to fill existing cavities in bone was not successful in any case in this series.

Complete excision of the lesion, whether of the bony or the soft tissues, as in the case of massive resection or sinusectomy, will produce an almost perfect result in practically all cases.

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Endometriosis of the Urinary Bladder

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IN 1921, Judd (*1*) published the first case of "Adenomyoma presenting as a tumor of the bladder." Until 1943, when Moore, Herring, and McCannel (*2*) presented a critical analysis of the literature, there were only 46 cases on record; since then 19 more cases have been added. The authors believe that this problem should be brought to the attention of the gynecologist as the recognition of the disease at the time of surgery and a knowledge of correct treatment are important to him as well as to the urologist.

CASE REPORT

D. W., a 29-year-old white gravida I, Para 0, was admitted to the hospital on 24 December 1948, complaining of a dull constant pain in the left lower quadrant of the abdomen with sharp knifelike exacerbations every 1 to 2 minutes, which lasted only a few seconds and radiated to the left flank. The pain was severe enough to double her up. There were no urinary complaints, no nausea or vomiting, but she had been constipated for the past 2 or 3 days. She stated that the pain was just like that which she had had in 1941 just before her right tube was removed for a ruptured ectopic pregnancy; the appendix had also been removed then.

Her last menstrual period was 17 November 1948 and was normal, lasting 2 days. Ten days prior to onset of the present illness she spotted for 2 days, but this was not as heavy as a normal period.

Her menarche was at the age of 18, her periods were regular, every 28 days, lasting 2 days. There was no dysmenorrhea, dysuria, hematuria, or other complaints. A review of systems was negative.

Physical examination revealed only questionable tenderness in the left lower quadrant of the abdomen. There was no rebound tenderness. (The patient was quite apprehensive and pelvic examination had to be done under sodium pentothal anesthesia.) Pelvic examination showed: external genitalia normal; Bartholin's and Skene's glands normal; vaginal and cervical mucosa clean; cervix somewhat dusky in color but otherwise normal; uterus small, hard, anterior, and movable; right adnexa, small and hard, a mass, 2×3 cm., probably ovary, was palpated; the tube was not palpable, left adnexa contained a soft mass, 3×4 cm., close to the uterus which was thought to involve the tube.

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Impression.—Left ectopic pregnancy, unruptured.

Laboratory data: Urinalysis was within normal limits; hemoglobin, 13 gm.; and red and white blood cell counts were within normal limits.

Operation.—The abdomen was opened through the usual lower midline approach. The right tube and ovary had been removed surgically. The left tube and ovary were adherent to the sigmoid and the sigmoid was kinked on itself by an adhesion to the left tube. The tube and ovary were freed from the bowel and a mass, 2×3 cm., was found lying under a vesico-uterine fold of peritoneum. A small piece of omentum adherent to this area was freed revealing a fixed mass underlying the peritoneum. There were no endometrial implants in the pelvis. An attempt was made to shell the mass out of the dome of the bladder where it seemed to lie; the bladder was entered because the mass apparently involved the bladder musculature. On opening the bladder the inner border of the mass, which contained numerous bluish cysts, could be seen lying submucosally. The first impression was that this was a neoplasm, but the possibility that it was an endometrioma was also considered. The mass and a margin of bladder wall were excised. The bladder was then closed around a No. 18 Foley catheter which was brought out through the lower end of the wound. The peritoneum was closed so as to extraperitonealize the cystostomy wound and the abdomen was closed in layers. A Foley catheter was also placed in the bladder through the urethra and continuous suction was applied to both catheters for 7 days. The wound healed primarily and the patient left the hospital on 13 January 1949, 18 days postoperatively.

Pathologist's report

One surface of the specimen is covered by mucosa beneath which are numerous cystic structures averaging 0.3 cm. in diameter and which have a reddish brown color.

Figure 1.—Endometriosis of the wall of the urinary bladder showing endometrial glands surrounded by endometrial stroma embedded in bladder musculature.

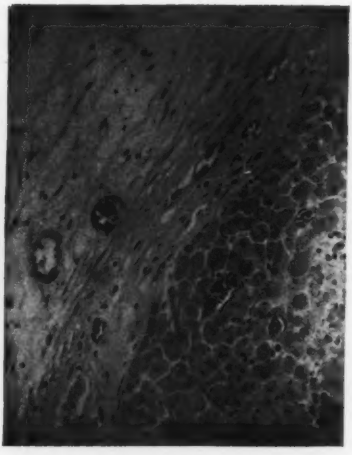

Figure 2.—High-power view of figure 3 showing fat and hemosiderin-filled macrophages in the cystic area.

Microscopic examination.—Sections of urinary bladder show small glandular structures deep in the muscularis. These are lined by cuboidal to columnar epithelium resembling that of the glands of the endometrium of the uterus (fig. 1). About these glands is a small amount of stroma consisting of densely packed hyperchromic ovoid cells. Those glands located toward the mucosa and beneath transitional epithelium are much larger and are lined by low cuboidal epithelium, and contain hemosiderin and fat-filled macrophages (fig. 2). The cellular response indicates old hemorrhage (fig. 3). Since the surface epithelium is intact, it is doubtful that hemorrhage occurred into the urinary bladder. In other areas there is dense fibrous tissue containing hemosiderin-filled macrophages, representing hemorrhage into stroma from ruptured glands with resultant scarring. The muscularis appears slightly hypertrophied throughout and the serosa is unremarkable.

Diagnosis.—Endometriosis of urinary bladder.

Figure 3.—Low-power view of bladder mucosa with a cystic area into which old hemorrhage has occurred.

DISCUSSION

There are four schools of thought as to the origin of endometriosis: (*a*) as a remnant of the wolffian (von Recklinghausen (*3*)) or Müllerian duct (Kossman (*4*)); (*b*) metaplasia from normal endothelial cells of the peritoneum, due to some hormonal or traumatic influence on the cells (Iwanoff (*5*)); (*c*) from normal endometrial tissue reaching aberrant positions as a result of direct extension (Cullen (*6*)), reflux of menstrual blood through the fallopian tubes (Sampson (*7*)), or by way of the lymph and blood vessels from the uterine cavity (Halban (*8*)); and (*d*) from derivatives of celomic epithelium (Waldeyer (*9*), Meyer (*10*), and Novak (*11*)). Each school of thought can produce cases to prove their theory and disprove the others so the question has yet to be settled.

Goodall (*12*) is a strong proponent of the third school. He believes there are two types of endometriosis depending upon the specific cell structure. The first type is called stromatous endometriosis because it comes from the stromal cells alone. The second type he calls the mixed type because it comes from the lining cells of uterine secretory glands and also has stromal cells present. As only the superficial layers of the endometrium respond to the monthly cycle, this holds for the ectopic cells as well. He indicates that there are three modes

of invasion of the bladder in the formation of an endometrioma. The first is direct, by lymphatic continuity or backflow from the deep uterine mucosa through the uterine wall. The second is indirect, from implants in the peritoneal vesico-uterine pouch and then into the muscularis and mucosa. The third is due to traumatic displacement of endometrial cells following surgery. He also divides bladder endometriosis into three groups. Group I is composed of cases of stromatous endometriosis and involves the trigone and base of the bladder derived directly from the deep layers of the uterine mucosa. Group II is composed of cases of involvement of the fundus from peritoneal endometriosis. The majority of these follow injury to the bladder at the time of surgery. Robert Meyer (*13*), in 1930, classified bladder endometriosis into three groups according to their origin: (*a*) internal endometriosis with origin probably from bladder epithelium; (*b*) external endometriosis with origin from serosal cells; and (*c*) collision endometriosis resulting from Groups I and II.

The case presented shows that there may be extensive involvement of the bladder without symptoms. However, this is a very rare occurrence in an uncommon disease entity. The classical picture is cyclic dysuria, urinary frequency, and hematuria. Hematuria associated with the menstrual period was present in only 13 of the 46 cases reported by Moore et al. (*2*). Urgency is usually associated with urinary frequency. Suprapubic pain with or without a menstrual period is also a common complaint. All the symptoms of pelvic endometriosis may be present and are an aid in the differential diagnosis. Relief of the symptoms during pregnancy is a good diagnostic sign, as is the cessation of the complaint with cessation of ovarian activity. The question of sterility is difficult to evaluate from the case reports in the literature, as that factor is usually omitted in the articles, but it is something to be aware of as possible diagnostic aid.

If endometriosis is suspected, cystoscopic examination should be done and, although a typical picture may not be present, the history and findings will usually indicate the correct diagnosis. Phillips (*14*) has an excellent series of colored plates demonstrating the typical cystoscopic findings.

The youngest patient was 18 and the oldest 48 years of age. The average age is between 35 and 39 years.

Keene and Kimbrough (*15*) in 118 cases of endometriosis, and Holmes (*16*) in 145 cases of endometriosis, each found bladder invasion in 2 cases.

The treatment of endometriosis of the bladder is dependent upon two things: the age of the patient and her child-bearing potentialities. If she is young and wishes to have children, then excision is

the treatment of choice, as the percentage of complete cures is very high. If the patient is approaching the menopause, irradiation of the ovaries to check ovarian activity is sufficient; regression of the lesion will follow and no further treatment is necessary. Castration by surgical means accomplishes the same end. Fulguration by the transurethral route is to be condemned according to Moore et al. (*2*).

If the patient is young and the lesion is too extensive for surgical extirpation or if the lesion is encroaching on the ureteral orifices, then the most effective treatment is castration.

The case reported presents several interesting features. At no time did the patient have any urinary complaints. Cyclic bladder complaints were present in 40 of the 46 cases reported upon by Moore et al. (*2*) and were present in every case reported since. Cystoscopic examination of this patient prior to surgery would have been interesting, but there was no reason to suspect bladder disease. It is unlikely that the vesico-uterine fold of peritoneum was damaged at the operation for ruptured ectopic pregnancy; however, in the series reported by O'Connor and Greenhill (*17*) of 58 cases of endometriosis of the bladder, 35 had had previous surgery; and the condition was most frequently seen following hysterectomy.

This patient had no other evidence of endometriosis.

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Hutchinson-Besnier-Boeck Sarcoid

Report of Three Cases and Review of the Literature

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THE word sarcoid was derived from the two Greek roots meaning "flesh" and "form." Boeck (*1*) called the disease sarcoid because he believed the histological picture resembled the small cells of sarcoma.

HISTORY (*2*)

In 1869 Hutchinson described the first case of skin involvement but failed to name the disease. In 1889 Besnier described lupus pernio and called it "Mortimer's malady" (after the patient's name). In 1889 Boeck described the disease and its histology under the title multiple benign sarcoid; later he called it "benign miliary lupoid." In 1902 Kienbock described the cystic bone changes but believed syphilis to be the cause. In 1915 Kutzinsky and Bittorf described the pulmonary lesions and correlated the skin with the lung lesions. In 1917 Schaumann integrated histologically the skin and lymph node lesions. In 1932 Kissmeyer summarized the previous contributions and added a few of his own. In 1936 Schaumann reported his 20 years of observation of the disease. In 1937 Longcope and Pierson (*3*) stimulated American interest in this disease.

CLINICAL ASPECTS

Sarcoidosis is usually a benign systemic disease involving the reticulo-endothelial system. This is a disease of the second and third decades with no sex predilection but with a greater incidence in the American Negro. The predominance of certain visceral involvement led to the description of several clinical entities.

Skin lesions appear in about 50 percent of patients with sarcoidosis. Some authors (*4*) (*5*) claim that when complicating visceral tuberculosis occurs the skin lesions may disappear.

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There are several specific dermatological manifestations of this disease:

(*a*) The Boeck-type (*1*) occurs most frequently in women. The areas involved include the face, especially the nose, mouth, and eyelids, the back of the shoulders, and the extensor surfaces of the arms. The lesions are papules, nodules, or infiltrating plaques; annular or gyrate. They are firm, elastic, round, and brownish-red. Occasionally telangiectases and superficial scaling occur. Sometimes under pressure the nodules seem to be composed of grayish-yellow foci which suggested to Boeck "miliary lupoid." When the lesions disappear atrophic pigmented areas remain.

(*b*) Lupus pernio (*6*) (*7*) is confused with chilblain lupus (Hutchinson), a type of discoid lupus erythematosus. The lesions are bluish-red, infiltrated, and in symmetrically placed plaques. The areas involved are the nose, ears, forehead, dorsal surfaces of the hands, and occasionally, the toes. Telangiectatic vessels are usually present over the surfaces of the lesions. The phalanges are often involved and present a fusiform deformity.

(*c*) The angiolupoid type was described by Brocq and Pautrier (*8*) in 1913 (*7*). The lesions are nodules and plaques; bluish-red occasionally tinged with yellow, and there are numerous telangiectatic vessels over their surfaces. They are located on the sides of the nose, inner ocular canthi, and cheeks.

(*d*) Erythrodermic type of sarcoid was described by Schaumann (*9*) in 1924. This form appears as large serpiginous, red scaling, noninfiltrating areas on the front of the legs and thighs. Pautrier described erythroderma of this type associated with lupus pernio of the face.

Nonspecific eruptions such as prurigo and urticaria may be present. Erythema nodosa may also be associated with this condition.

(*e*) In 1906 Darier and Roussy (*10*) (*11*) described a type of sarcoid. The lesions consisted of painful nodules in the hypoderm in areas of adipose tissue. They sometimes occur in chains following the blood vessels. This causes confusion with erythema induratum which some authors believe to be a sequela of this type of sarcoid. The lesions are limited to the trunk and lower limbs. They vary in size from a bean to a walnut and in color from that of normal skin through different shades of red. Occasionally they flatten out to form plaques. They are usually numerous, never ulcerate, or metastasize and, when they subside, fibrosis may result. This type of sarcoid is now being recorded more frequently with the Boeck type.

There are two skin diseases which have frequently been erroneously classified as cutaneous sarcoid. These are the sarcoid-type of tuberculosis of the American Negro and the sarcoid of Spiegler-Fendt.

Nomland, Crawford, Klauder, and Thomas (*12*) believe that the sarcoid-type of tuberculosis of the American Negro is tuberculosis of the skin of hematogenous origin which assumes sarcoid features due to an unusual immunological reaction on the part of the patient. Thomas presented 11 cases illustrating five main types of cutaneous lesions. The superficial lesions, which on healing left atrophic scarring, resembling discoid lupus erythematosus. The small papules about the eyes, nose, and mouth resembled psoriasis. There were brownish indurated plaques assuming annular configuration with central atrophy. The nodular ulcerative lesions on the legs resembled, in appearance and course, those of erythema induratum. There were also subcutaneous cherry-sized nodules on the body. Reisner (*13*) described cutaneous tuberculosis in the American Negro as having the following characteristics: sarcoid-type of skin lesions; skin histologically on a borderline between sarcoid and tuberculosis; positive tuberculin test; and, in some patients, subsequent caseous tuberculosis in various viscera.

The sarcoid of Spiegler-Fendt actually is lymphosarcoma. Spiegler and Fendt realized that they were not dealing with sarcoma and called the lesions a type of "sarcoid." In 1935 Lewis (*14*) reviewed the literature and summarized his impressions. There are two types of lesions: the localized superficial benign type, which may disseminate; the lesions are few in number, tend to be grouped, appear in any part of the body, and resemble the miliary sarcoid of Boeck; the disseminate type has varying numbers of nodules, plaques, and tumors which vary from the color of skin to reddish-blue, occur anywhere on the cutaneous surface, and may involve any organ of the body. All of these types are histologically reticulum cell lymphosarcoma. The outcome in the disseminate type may be unfavorable. There is an absence of the clumping of the naked nuclei of granuloma fungoides, of intracellular nuclear proliferation of lymphogranulomatosis, and of the Dorothy-Reed cells of Hodgkin's disease.

The diagnosis of systemic sarcoidosis is made from the clinical picture, radiological examination of the chest and small bones, anergic reaction to high concentrations of tuberculin, absence of tubercle bacilli in involved areas, and skin biopsy. The signs and symptoms depend on the organs involved. There may be fever (unusual), generalized malaise, fatigue, and weight loss. The skin, eyes, salivary glands, lungs, bones, and lymphatic system are the more common sites of involvement; however, hypophyseal (*15*), tonsillar (*9*), laryngeal, breast, cardiac (*16*), intestinal, pancreatic, and testicular infiltrations have been described.

Uveoparotitis was described in 1909 by Heerfordt (*17*). He designated the inflammation of the parotid gland and the iris as a localized type of sarcoid. This phase of sarcoidosis occurs in about 10 percent.

Other salivary glands may be involved. Fever may precede or accompany the early stages. The firm and painless swelling of the parotid gland usually precedes the ocular involvement. The inflammation of the parotid gland is confined to the capsule and may persist from 2 to 6 months. The uveitis is the most common ocular lesion; however, corneal herpes, corneal opacities, vitreous hemorrhages, optic neuritis, chorioretinitis, glaucoma, nodular conjunctivitis, and infiltration of the adnexa have been described (*18*). In one-third of the cases facial nerve paralysis occurs, and in one-half of these cases it is bilateral. Erythema nodosum or toxicum has been described as accompanying some of these cases. This disease has been classified under Mikulicz's syndrome because symmetrical lacrimal and parotid gland involvement has been described.

In 1924 Martenstein (*19*) found the roentgenographic incidence of hilar involvement to be about 31 percent. He described the characteristic roentgenographic lesions to be enlarged hilar nodes, atelectasis, chronic interstitial fibrosis, and the "ground glass effect." King (*20*), and Bernstein and Sussman (*21*) have described the roentgenographic chest findings. Leitner, Bernstein, and Sussman (*21*) and Rubin (*22*), classified the roentgenographic features into phases for descriptive purposes, but one must remember the lung changes are not static and that the pulmonary picture is usually changing from one phase into another. Three phases of pulmonary involvement are described. The hilar phase is the most common and can usually be seen in a chest roentgenogram. The hilar lymphadenopathy, which is usually bilateral and symmetrical, involves both peribronchial and right peritracheal nodes. The transitional phase develops with diminution of hilar lymphadenopathy and the infiltration of the adjacent parenchyma. The process, unlike tuberculosis, spreads to the middle and lower lobes. In erythema nodosum similar hilar adenopathy has been described but the skin lesions and the course of the thoracic lesions are important differential points. The parenchymal phase is characterized by reticulation, stippling, or marbling. Infiltration is greatest in the middle and lower lobes. This phase poses roentgenologic diagnostic problems. The reticulation resembles lymphangitic carcinoma; the stippling resembles hematogenous tuberculosis; and the marbling resembles metastatic carcinoma. The pleura is often involved but pleural effusion is rare unless there is the complication of heart failure or active tuberculosis. With massive parenchymal involvement, this disease can resemble any fibrosing or ulcerating lung disease but the roentgenologic picture is out of proportion to the patient's symptoms.

In 1934 Nielsen reported the incidence of bone lesions to be 20 percent. Schaumann (*5*) believed that the marrow is the starting point

of sarcoidosis. In 1919 Jüngling called the lesions "osteitis tuberculosa multiplex cystoides." In 1931 Kirklin and Morton (*23*), and in 1938 Ellis (*24*) described the lesions accurately. The two pathologic findings are a thickening of the trabeculae and clear cystic changes. The phalanges of the hands and feet are almost always involved. Skin lesions are usually present. The lesions occur predominantly in young adults. There is no sinus formation, sequestration, joint, or periosteal involvement. The lesions must be differentiated from tuberculous or syphilitic dactylitis, blastomycosis, chondromatosis, and osteitis fibrosa cystica.

Boeck noted the lymphadenopathy in his original description. Schaumann (*5*) described this disease as an affection of the lymphohematopoietic system exhibiting lesions of the cutaneous and visceral lymphatic structures.

Of the cases of sarcoidosis about one-third to one-half will undergo spontaneous healing. In the remaining half, 50 percent may become chronic and show organic involvement of irreparable nature and the other 50 percent may develop tuberculosis. As Rubin and Pinner (*25*) stated the benign nature of this disease has been overemphasized. The causes of death in sarcoidosis are complicating tuberculosis, dysfunction of vital organs through invasion, pulmonary infarction, and widespread amyloidosis.

Consideration of the differential diagnoses must include the following:

Skin diseases	*Systemic disease*
Nodular-type of discoid lupus erythematosus.	Tuberculosis.
Erythema induratum	Hodgkin's disease.
Hodgkin's disease of skin	Deep fungus infections:
Nodular tuberculosis	Coccidioidomycosis.
Mycosis fungoides	Aspergillosis.
Leprosy	Chemical granulomatoses:
Syphilis	Berylliosis.
Neurofibromatosis	Silicosis.
Leukemia cutis	Asbestosis.
Lymphangioma cutis	Syphilis.
Multiple lipomas	Leprosy.
	Gonorrhea.
	Gout.
	Lymphatic leukemia.
	Lymphosarcoma.
	Metastatic carcinoma.

ETIOLOGY

Most investigators believe the etiologic factor to be a reaction of immunity to the tubercle bacillus or its products. Darier classified Boeck's sarcoid with the tuberculids. Pinner (*4*) believes that sarcoid is noncaseating tuberculosis and that the noncaseating lesions may

undergo caseation. Reinstierna and Filho (*26*) believe that the whole picture can be produced by leprosy. Schaumann (*5*) believed the bovine bacillus to be responsible. Snapper advanced a virus as the cause. Kveim made an antigen from lymph nodes of patients with sarcoid thinking that sarcoidosis might be a virus disease like lymphopathia venereum. He believed his skin test to be as specific and allergic as the Frei test; however, the usefulness of the test is hindered because of lack of standardization and the occasional slow response to the test.[2]

In view of the failure of animal inoculation, the problem is to explain the negative tuberculin test. Sulzberger (*27*) found that in persons with sarcoidosis the tuberculin test was negative more often than in healthy persons. Leider (*28*) and others explain the anergic state as a specific alteration in the capacity of tuberculous patients to react to tuberculin. In 1921 Martenstein advanced the idea that the negative tuberculin test in those patients resulted from the presence in the blood serum of tuberculin neutralizing factors known as "anticutins." Pinner, Weiss, and Cohen demonstrated the presence of "anticutins" in the serum of 5 percent of normal and tuberculous patients, and in 36 percent of the patients with sarcoidosis. The presence of "anticutins" in sarcoid was found less frequently than the negative tuberculin test. Other authors have not been as successful in demonstrating these "anticutins."

HISTOLOGY

The basic histologic lesion is the "hard tubercule." Under the microscope one sees a uniform and monotonous picture. The characteristic lesion is a circumscribed collection of epithelioid cells with a few scattered Langhans-type of giant cells and a lack of lymphocytic response. Central necrosis or caseation is always absent. The microscopic picture of sarcoid must be differentiated from that of tuberculosis. Caseation or polymorphonuclear response of tuberculosis does not occur in sarcoid. The giant cells of sarcoid differ from those of tuberculosis in that they are larger, more nucleated, seldom arranged in elliptical manner, and contain Schaumann's inclusion bodies. A greater uniformity of proliferative type of tissue response is seen in sarcoid. The lesions of the liver, when involved in sarcoid, occur in the portal triad with only a few in the midzones of the lobules while the reverse is true when the liver is involved in tuberculosis. Unlike tuberculosis, the reticulum is not destroyed in sarcoid.

LABORATORY DATA

Harrell and Fischer (*29*) have reported hyperproteinemia, hyperglobulinemia, increased blood calcium and phosphatase in the active

[2] It may sometimes take as long as 6 months for a positive Kveim test to develop.

cases; the blood chemistry values become normal when the lesions heal. Reisner (*13*) stated that monocytosis occurs more frequently in the early or the disseminating phase. There is usually an eosinophilia and an elevated sedimentation rate which will persist even in the asymptomatic chronic phase. A false positive blood Wassermann test is found occasionally. In uveoparotid fever there may be a pleocytosis and an increased protein in the cerebrospinal fluid. Other changes in the blood picture and chemistry may result from the infiltration of vital organs such as massive pulmonary involvement with secondary polycythemia.

TREATMENT

The treatment of this disease is at best palliative and symptomatic. In the generalized type, arsenic has been used, but the hazard of large doses over long periods of time must be recognized. High voltage roentgen therapy has proved beneficial occasionally for the skin lesions, but it is of questionable value for systemic involvement; Pohle, Paul, and Clark (*30*) had favorable results in 8 of their 14 cases with hilar adenopathy. They had no therapeutic complications and advocated further use for true clinical evaluation. Lupus pernio is best treated with intensive applications of carbon dioxide. Gold, sodium thiosulfate, bismuth, tuberculin, and chaulmestrol have been used with no remarkable or consistent results. Curtis, Taylor, and Grekin (*31*) have reported favorable results from the oral administration of calciferol and dihydrotachysterol, working on the theory that increased excretion of phosphorus might affect the phospholipins.

CASE REPORTS

Case 1.—I. V., a 23-year-old Negro, was first seen in the out-patient clinic on 3 August 1948 complaining of dyspnea on exertion for 5 weeks. The patient had noted an increase in the dyspnea since 20 July 1948 when he developed an upper respiratory infection with a productive cough and greenish-yellow sputum.

A chest roentgenogram (fig. 1) showed a roughly rounded area of increased density extending from the right upper paravertebral area toward the right hilum in the region of the fourth, fifth, and sixth posterior interspaces and lying above the right first rib and upper border of the right second rib to the right of the midline. The lateral view showed the area of density to be in the anterior portion of the superior mediastinum without displacement of the trachea and esophagus. The remainder of the lung fields were clear. It was thought that the new growth of the mediastinum was probably of the lymphoblastoma group.

The patient was admitted to the Naval Hospital, Philadelphia, for further study on 10 August 1948. On admission his complaints were substernal pain, which began 7 August 1948, dyspnea on exertion, and a productive cough with greenish-yellow sputum.

The past and family histories were noncontributory.

Physical examination.—The patient was a Negro in no apparent distress. His eyes, ears, nose, and throat were normal. There were several small lymph nodes which were nontender, not fixed or discrete in the right axilla, both right

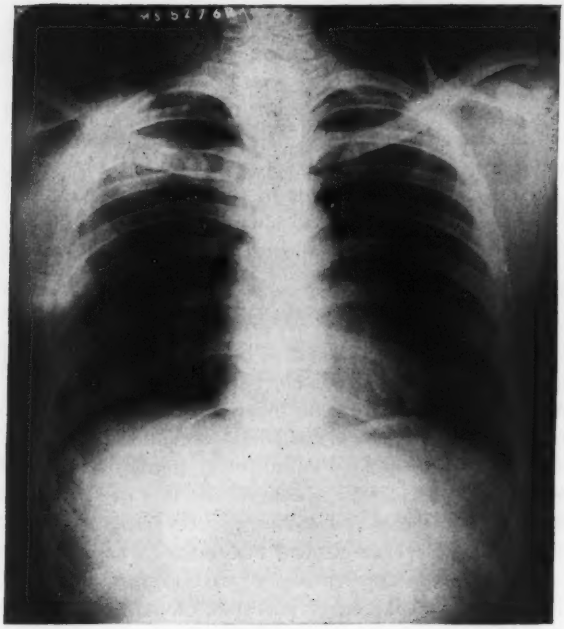

Figure 1.

and left inguinal regions, and left supraclavicular fossa. Examination of the lungs and heart revealed no abnormalities. Blood pressure was 130 systolic and 70 diastolic. Examination of the abdomen, genitalia, and extremities was essentially negative.

Bed rest and a regular diet was prescribed. On 20 August 1948 a biopsy of a lymph node from the left supraclavicular fossa was suggestive of sarcoidosis but tuberculosis could not be ruled out. A second biopsy of the right axillary node on 30 August 1948 when compared with the previous biopsy indicated sarcoidosis. Chest roentgenograms during hospitalization revealed no change from the previous films. Roentgenograms of the hands and feet revealed no rarefaction of bone.

Tuberculin test, blood Kahn test, and urinalysis were negative. Red blood cell count, 4,500,000; hemoglobin, 13 gm.; white blood cell count was 4,700, and the differential was normal. The blood calcium, total serum protein, albumin, and globulin were normal.

The patient's course in the hospital was uneventful and his symptoms disappeared almost entirely with symptomatic therapy. The final diagnosis was sarcoidosis involving the paratracheal nodes and the subcutaneous lymph nodes.

Case 2.—S. B., a 24-year-old Negro was admitted on 22 June 1948 complaining of dyspnea on exertion. He had no complaints until January 1946 while in the Army, at which time he had a cough, expectorating small amount of white mucus and moderate dyspnea. In February 1946 a chest roentgenogram showed lesions suggestive of tuberculosis; as a result, he was hospitalized. Studies at that time were negative for tuberculosis. He was discharged from the hospital

and from the Army after several months hospitalization. Sarcoidosis was the tentative diagnosis.

By November 1947, the dyspnea and cough had increased and he was again hospitalized. At that time chest roentgenograms revealed some increase in the pathologic lung changes with suggestion of cavity formation; the lesions were diffusely scattered throughout both lungs. Studies for evidence of tuberculosis were again negative. No positive results were obtained from tests for fungus disease. Bronchoscopic examination revealed no abnormalities. A biopsy of an enlarged lymph gland showed lymphadenitis. After several months he was discharged from the veterans' hospital with a tentative diagnosis of sarcoid disease.

The patient's symptoms continued. He had progressive weakness, weight loss, night sweats, and occasional chest pain. He was again hospitalized in June 1948, as he had lost 10 pounds in the previous 3 months and was unable to work. Treatment gave him no relief.

On admission in June 1948; the patient was a poorly nourished Negro and was in only slight distress. The positive physical findings were signs of consolidation throughout the right lung field and the upper portion of the left lung. There were several small discrete lymph nodes in the right supraclavicular region. No other abnormal findings were noted. His temperature (98.6° F.), pulse rate (96), respirations (18), and blood pressure (120/80) were normal.

Roentgenograms of the chest (fig. 2), showed the entire right lung field up to the apex to be almost obliterated by patchy areas of homogenous densities.

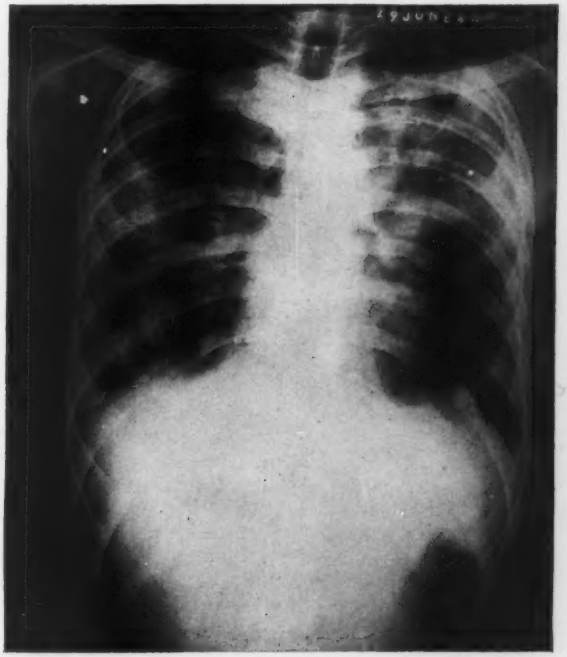

Figure 2.

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The upper left and left midlung fields were also obscured by similar patchy areas of homogenous density, but the parenchymal markings were visible. There was no evidence of abnormality in the region of the heart or great vessels.

White blood cell count on admission was 7,100; differential count showed 10 young and 62 old polymorphonuclears, 18 lymphocytes with 10 monocytes. Red blood cell counts, 4,200,000 with a hemoglobin of 9 gm. The urinalysis and blood Kahn test was negative. Repeated gastric washings and sputum analysis revealed no tubercule bacilli or fungi on smear or culture. Skin tests for tuberculosis, coccidioides, and histoplasmosis showed no reaction. Sedimentation rate was 21 mm. in 30 minutes (Cutler) with a maximum of 5 mm. in 5 minutes; this remained elevated throughout hospitalization. The blood calcium, total serum protein, albumin, and globulin were within normal limits.

It was thought from roentgenographic findings and the past medical history, that the patient might have active tuberculosis. However, roentgenographic findings were also compatible with sarcoidosis. During his course in the hospital, his temperature ranged from 98.6° to 102° F. with an accompanying increase in pulse rate. With bed rest and symptomatic therapy improvement was noted; repeated roentgenograms and physical examination showed no change.

On 2 September 1948, a supraclavicular lymph node, 10 mm. in diameter, was removed for biopsy. On cut section it was grayish-pink, and histological examination revealed tissue characteristic of Boeck's sarcoid.

The patient was thoroughly examined for other evidence of sarcoid by an ophthalmologist and a dermatologist. No abnormalities were noted. He was discharged on 10 September 1948 with orders to return for periodic chest roentgenograms and physical examinations to determine the status of the sarcoidosis. Some dyspnea on exertion still persisted at the time of discharge.

Case 3.—J. M. B., a 25-year-old white man was admitted on 15 March 1948 for study. Routine chest roentgenogram taken on 10 March 1948 (fig. 3), at his place of employment revealed an extensive mediastinal mass with widespread scattered areas of soft density throughout the upper chest, bilaterally. A chest roentgenogram taken on 20 January 1947 had been reported as negative. Apparently the patient had been perfectly healthy until January 1948 when he first complained of pain in the upper lumbar region bilaterally which radiated anteriorly along the lower costal margin. This pain lasted 1 week and had recurred several times. The patient had lost 16 pounds since the onset of the pain. Progressive weakness was noted in this same period. No dyspnea, cough, or other symptoms referable to the lungs were present.

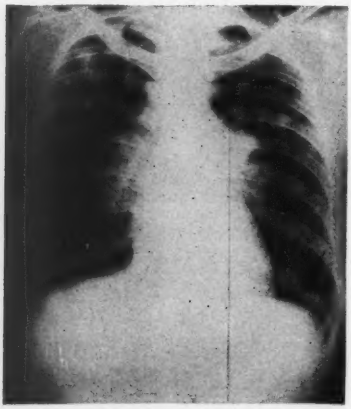

Figure 3.

Past and family histories were noncontributory.

Physical examination on admission revealed a tall, well-developed white man weighing 199 pounds. The ears, eyes, nose, and throat were essentially negative. Examination of the chest revealed no abnormal findings. The liver and spleen were not palpable and there was no tenderness in the abdomen. The genitalia and extremities

were normal. No lymphadenopathy was noted. His blood pressure, pulse rate, temperature, and respirations were normal. At this time it was thought that the mediastinal mass could be Hodgkin's disease, sarcoid, metastatic carcinoma, or tuberculosis.

Studies were begun to make the correct diagnosis. White blood cell count, 5,700 with a normal differential. Red blood cell count, 4,500,000 with hemoglobin 13 gm. Urinalysis and the blood Kahn test was negative. The total serum protein, albumin, globulin, and blood calcium was within normal limits. The sedimentation rate was slightly elevated. The tuberculin test was negative in 1 : 100 and 1 : 1000 dilution.

Roentgenograms of the chest were compatible with sarcoidosis. Roentgenograms of the hands and feet were negative. An intravenous urogram was within normal limits. An incidental finding at that time was spina bifida occulta of the first sacral segment with moderate demineralization of the lumbar spine.

Bronchoscopic examination on 1 April 1948 showed the carina to be greatly deformed and broadened. The entire area at the angle of the main bronchi was distorted and the lumina narrowed. It was thought that this was caused by a smooth swelling in the region of the mediastinum apparently spreading the bronchi. Papanicolaou stain of bronchial secretions was reported as negative for tumor cells.

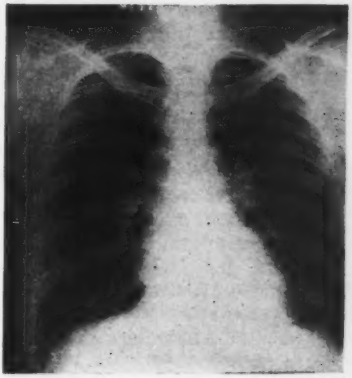

Figure 4.

No positive diagnosis could be established after the completion of the studies. It was believed that the patient's condition was probably Hodgkin's disease or sarcoidosis. He was seen by a group of consultants who thought that high voltage roentgen therapy to one side of the chest should be given to see the effect on the mediastinal mass and the lung. Dosage was to be 100 roentgen anteriorly and posteriorly to the right hemothorax on a 15 by 15 cm. field, and this was to be given at monthly intervals for 4 months and then a free interval of 4 months was to be allowed to lapse before a possible second course was to be instituted. This therapy was begun on 18 April 1948. He had made clinical improvement on symptomatic therapy and bed rest. There were no changes in the physical findings or chest roentgenograms on discharge.

The patient continued working while receiving therapy, until 9 August 1948, when he had an acute gastroenteritis. He was admitted to the hospital on 13 August 1948, still complaining of anorexia and vomiting. Vague lumbar pain had persisted since his previous admission. Physical examination at this time revealed no change from his last admission except for some mild epigastric tenderness. With diet and symptomatic therapy he soon recovered from this acute gastrointestinal upset.

On admission white blood cell count was 15,000 with an increase in polymorphoneutrophils: this was normal in 1 week. Tuberculin tests were still negative. Other laboratory tests were within normal limits.

A chest roentgenogram (following the last high voltage roentgen therapy) on 24 August 1948 showed a considerable decrease in the bilateral peribronchial

density and adenopathy and the soft nodular involvement of the apical regions (fig. 4). Roentgenograms of the bones of the hands and feet revealed no change.

On 3 September 1948, a small discrete lymph node was noted in the right supraclavicular region. On 10 September 1948 a biopsy showed histologically typical Boeck's sarcoid. With the diagnosis established, the patient was discharged to be checked at frequent intervals by chest roentgenograms and physical examinations.

SUMMARY

Three cases illustrating sarcoidosis involving the lungs and peripheral lymph nodes are presented; the diagnosis in each of these cases was confirmed by lymph node biopsy although the condition was suspected following chest roentgenograms. Sarcoidosis can involve almost any organ in the body and can present many different signs and symptoms, and should be kept in mind when making a differential diagnosis in certain symptom complexes.

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Carcinosarcoma of the Uterus

Report of a Case

ALAN RAFTERY, *Lieutenant (MC) U. S. N.*[1]

EWING (*1*) devotes a section of his discussion of types of sarcoma to carcinosarcoma of the uterus, emphasizing errors in interpretation. In 1938, Saphir and Vass (*2*) reviewed 36 cases of carcinosarcoma occurring in the uterus and did not believe any of these to be true coexisting carcinoma and sarcoma, pointing out the common sources of error in interpretation. Since that review 2 cases have been reported in the English literature (*3*) (*4*). The following case is reported not only because of the rarity of the condition, but also to point out an error in interpretation, the antithesis of those emphasized in the references previously mentioned.

CASE REPORT

A 62-year-old white woman was admitted in January 1948 complaining of slight vaginal bleeding of 3 months' duration. Cytologic study of vaginal smears showed malignant cells, probably of endometrial origin (fig. 1). Tissue obtained by uterine curettement showed adenocarcinoma of the endometrium (fig. 2).

She received 5,000 mg. hours of radium by intrauterine application. Six weeks following the completion of radiation a total hysterectomy was performed. The uterus showed a necrotic, boggy, papillary mass, 3.0×2.5×2.5 cm. attached by a short pedicle, 1.2 cm. in diameter, to the endometrium in the center of the anterior uterine wall. Sections from this mass and the adjacent uterine wall showed a few nests of degenerative-appearing epithelial cells embedded in degenerative stroma. The base of the stroma was cellular with extreme inflammatory cell infiltration and the stromal cells showed considerable radiation effect. The postoperative course was uneventful and the patient was discharged.

In August 1948 she was readmitted complaining of a recurrence of vaginal bleeding. On examination, a large soft hemorrhagic mass was found in the vaginal vault; on biopsy this was found to be an anaplastic sarcoma. At this time sections of the original specimen and others from the uterus were carefully reviewed. The stromal reaction noted in the original reports was interpreted at this time as sarcoma and the diagnosis was changed to carcinosarcoma of the uterus.

The tumor in the vaginal vault did not respond to high-voltage roentgen therapy and progressively enlarged. Her course was steadily downhill; partial bowel and ureteral obstruction and a rectovesicovaginal fistula occurred and the patient died 9 January 1949.

[1] U. S. Naval Hospital, Bremerton, Wash.

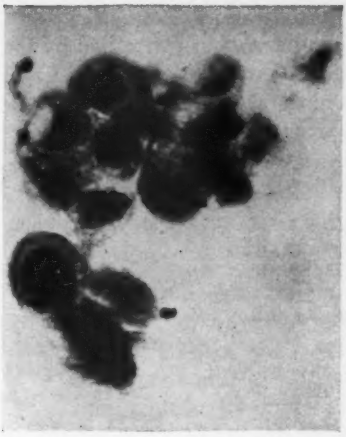

Figure 1.—Malignant cells in original vaginal smear. × *400.*

Figure 2.—Original endometrial biopsy. × *250.*

At autopsy the pelvis was found to be filled with a huge necrotic tumor mass that involved the pelvic structure and displaced the urinary bladder. The rectum and bladder opened into a cavity 22 cm. in circumference lined on one border by recognizable vaginal mucosa. Numerous sections taken from the mass showed a picture of an anaplastic sarcoma characterized by cellular pleomorphism, lack of differentiation, and broad areas of necrosis (fig. 3). A single tumor nodule, in the lower lobe of the right lung was found; histologic examination showed a well-differentiated metastatic adenocarcinoma, resembling the adenocarcinoma of the uterus seen in the first biopsy (fig. 4).

Figure 3.—Pelvic sarcoma at autopsy. × *250.*

Figure 4.—Metastatic adenocarcinoma, lower lobe, right lung. × *125.*

COMMENT

It is believed that the intrauterine carcinoma was controlled by the initial radium therapy, but the radioresistant sarcoma survived and gave rise to the "dropped" metastasis in the vaginal vault. The pulmonary metastasis probably occurred prior to instituting therapy.

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AN ARTIFICIAL HEART OR CARDIOPULMONARY MACHINE; Performance in Animals, by V. O. Bjork. From the Surgical Clinic of Sabatsberg Hospital, Stockholm, Sweden. Lancet **2**: 491–493, Sept. 25, 1948.

Bjork reports that in 1935 Crafoord found that it was possible to suspend the flow of blood to all the organs except the brain for a considerable period of time without damaging them. In 33 patients undergoing operation for patent ductus arteriosus he double clamped the aorta just below the point where the left subclavian artery arises for from 10 to 27 minutes without producing any disturbance in the internal organs of these patients.

In 1946 Crafoord and Anderson constructed an artificial heart which Bjork used in the dog. He clamped both the inferior and superior venae cavae for 33 minutes rendering the heart bloodless but maintaining the blood flow to the brain with the artificial heart. The dog survived with no evident signs of organic damage. They state that in order to perform a bloodless intercardiac operation it is only necessary to maintain an adequate circulation of oxygenated blood through the brain and to provide for maintenance of the blood concentrates within normal limits.

The apparatus consists of a horizontal cylinder containing a partition trough in the lower part of the cylinder. The blood flows alternately over successive partitions and through the cylinders; runs a central axle bearing 40 to 50 rhodium-plated stainless steel disks which dip into the blood and as they rotate expose films of blood to the oxygen in the cylinder.—*Abstract.*

Disinsertion of the Biceps Brachii

Report of a Case

JOHN S. THIEMEYER, JR., *Commander (MC) U. S. N.*[1]

DISRUPTION of the continuity of the biceps brachii muscle is common among persons such as laborers and athletes, and others performing strenuous muscular exertions. Commonly, the disruption occurs in the continuity of the long head.

Gilcrest (*1*) reported a series of 100 cases in which rupture in 20 occurred in the upper musculotendinous junction and in 56 involved the long head directly as follows: rupture of long head, complete in 3; rupture of long head, partial in 5; rupture of tendon of long head (intra-articular portion) in 34; and rupture of tendon of long head (extra-articular portion) in 14. There were also 2 with rupture of lower musculotendinous junction; 1 with rupture of lower tendon itself; and 3 with rupture of lower tendon, lower attachment.

Thus, there were only 6 cases in which the lower tendon was involved and only 3 cases in which the lower attachment was involved.

Watson-Jones (*2*) states "although the distal tendon is exposed to similar muscle strains, it is not subject to pathological degenerative changes and less than 40 cases of ruptures or avulsion have been recorded."

Milch (*3*) reported a case of "disinsertion of the biceps brachii" in April 1948 which presented the typical "lumping" of the muscle at the upper arm which occurs in disinsertion of the distal portion of the muscle. This case was operated upon and the muscle reinserted by means of a fascial graft.

CASE REPORT

A. J. P., a 43-year-old man, had pain of the right arm following lifting of a heavy table. A "tearing" sensation occurred at the same time and the patient felt as though he had "torn his shirt." Upon looking at his arm he noticed the "muscle all bunched up" at the upper end of his arm and he became alarmed.

His past and family histories revealed no significant findings and a complete blood count and urinalysis was within normal limits. The blood Kahn

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Figure 1.—Depression above the antecubital fossa and massing of the biceps muscle in the anterior-superior arm. This photograph taken when patient was anesthetized does not show the marked "bunching" of the muscle which was seen on admission.

test was negative. Roentgenograms of the entire arm and forearm showed no evidence of pathologic bone changes.

Physical examination: The patient was a robust, well-muscled, white man not appearing in acute distress. The right arm showed massing of the biceps muscle in the anterior-superior surface of the arm with a definite depression above the antecubital fossa (fig. 1).

Flexion and extension at the elbow joint was full actively but flexion was weak and painful against resistance. Active pronation and supination were weak, although nonpainful.

Palpation of the muscle mass elicited an "annoying" sensation but not a painful one and a firm, freely-movable mass about the size of a 25-cent piece, which was believed to be the distal end of the biceps tendon, was palpated at the distal pole of the mass. At surgery this proved to be the case.

Shoulder motion was full and painless in all planes.

Surgery was performed the following morning. Under a pneumatic tourniquet a "bayonet" or Z incision was made with the proximal arm along the mesial surface of the arm; the transverse arm crossing the antecubital fossa and the distal arm along the upper one-third of the lateral forearm.

Upon dissecting through the sheath of the biceps brachii proximally, a moderate semiorganized blood clot was encountered and the muscle itself was seen to be moderately hemorrhagic and retracted. The distal tendon was coiled in the lower pole of the sheath cavity and was found to be freely movable. A clamp was placed over the end of the tendon and it was withdrawn from the wound (fig. 2).

Dissection was then carried down into the forearm and the site of attachment of the biceps brachii to the ulna was exposed, showing an irregular, fibrous tissue surface from which the tendon had become disinserted. A drill hole was passed through the ulna at this point and the biceps tendon passed down through its channel and secured to its normal insertion by No. 1 braided silk sutures. In addition several silk No. 00 sutures secured the tendon to the periosteum. The frayed tissue of the remnants of the lacerated fibers were sutured together. The wound was then closed in an anatomical manner and an ace bandage and sheet wadding dressing applied from knuckle-line to upper arm. Over this dressing a posterior molded splint was placed with the elbow in maximum flexion.

Figure 2.—Surgical exposure of disinsertion of the biceps brachii from the ulna insertion.

The patient remained in the posterior splint for a period of 1 month following which progressive return of function was carried out.

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INTRA-ARTERIAL BLOOD TRANSFUSION, by Sam F. Seeley, *Colonel, MC, U. S. A.* American Journal of Surgery 78: 733–735, Nov. 1949.

One of the most important considerations in the prevention of shock or the treatment of circulatory collapse is the appraisal of the disparity between vascular volume and the capacity of the vascular system. Because of the difficulties encountered in estimating the degree of depletion of the vascular volume, work on the intra-arterial administration of blood was begun in 1939. If a reservoir containing blood is attached to a major artery the supply of blood from the reservoir may be regulated to maintain normal blood pressure and to replace blood loss from hemorrhage.

Blood has been administered by way of the aorta, femoral, dorsalis pedis, brachial, and radial arteries. No damage to the arteries has been reported as a result of insertion of the needle. The hazard involved in the administration of blood of low oxygen content within an artery in the distal extremity may be overcome either by oxygenation of the transfused blood or by the introduction of a catheter of sufficient length into the radial artery to deliver the blood at or near the aortic arch. Attempts to oxygenate blood so far have not been successful. Arterial administration of blood is of value in (*a*) replacing rapidly large quantities of blood in cases of severe hemorrhage; (*b*) replacing sufficient blood to maintain blood pressure levels in cases of concealed hemorrhage; (*c*) maintaining normal blood pressure levels in the presence of impending collapse caused by trauma or hemorrhage so that surgery may be performed promptly when indicated; (*d*) perfusing patent coronary vessels at a blood pressure of any desired level, in cases of coronary infarction; (*e*) reducing blood pressure, to any desired level consistent with tissue oxygenation, during the stage of operation where serious hemorrhage may be expected with the subsequent return of blood to the circulation after the stage of danger has passed; and (*f*) producing a blood pressure level in the distal aorta equal to that of the proximal aorta prior to the release of clamps after resection of the aorta in cases of coarctation.—*Abstract.*

Tetraethylammonium Chloride in Pain

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PAIN following needle aspiration of material for liver biopsy has not seemed to be a serious complication nor a contra-indication to the use of this diagnostic method. Nevertheless, pain of various intensities is reported to follow removal of a specimen for liver biopsy in as many as 80 percent of cases (*1*). This is particularly true when the transthoracic approach is used. Indeed, this has led many clinics to the routine use of demerol or morphine as a preoperative measure to minimize possible discomfort to the patient (*2*). Since the patients selected for liver biopsy are likely to be overly sensitive to opiates or barbiturates, it is desirable to use other means of analgesia, particularly in the small group of patients who experience severe pain following the operative procedure.

At the Army Hepatic and Metabolic Center specimens for liver biopsy are obtained through the thorax with the Vim Silverman needle. In this series three sites of pain have been noted even with the use of demerol preoperatively. First, pain in the epigastrium or right upper abdominal quadrant may be noted immediately with insertion of the needle. This has been described as dull and usually lasts about 2 hours, but may persist for a longer period. It may be associated with nausea lasting for a few minutes to 2 hours. This pain, even when persistent, is usually a source of only mild complaints by the patient. Second, a rather common and distressing pain has its onset from a few minutes to an hour following needling. This is a sharp, shooting, pleuritic pain aggravated by inspiration. It is usually located at the site of needle insertion and may radiate through to the back or upward to the right shoulder and when present the patient's breathing is shallow and he splints his right hemithorax. This pain may be so severe that the patient is able to speak only in a

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grunting manner and he becomes extremely apprehensive because of his inability to fill his lungs with air. It is this type of pain for which some form of relief is desirable. The third and least common site of pain in this series has been the right shoulder pain; usually it is mild and referred to the right supraclavicular fossa. This pain has never been noted in the absence of the pleuritic pain although it is not necessarily present with the pleuritic pain.

Tetraethylammonium chloride was used at this hospital for the relief of pleuritic pain secondary to pulmonary infarction and it was believed that a trial with this drug was warranted when pleuritic pain occurred after obtaining a specimen for liver biopsy is obtained.

We have used tetraethylammonium chloride for the relief of pain in 28 patients who had sufficient pain to require some form of analgesia (table 1). One of these was given the drug prophylactically. In 23 patients there was at least 50 percent relief from pain with the intravenous administration of from 75 to 200 mg. of the drug. Seven experienced temporary relief and required a second injection to gain permanent relief. One patient obtained less than 50 percent relief from pain, but with a second administration attained 90 percent relief

TABLE 1.—*Results with tetraethylammonium for relief of postbiopsy pain*

Patient	Age	First dose	Percent of relief	Duration of relief	Second dose	Percent of relief	Duration of relief	Comment
		Mg.			*Mg.*			
1	25	200	80	15 minute	200	90	Permanent.	
2	22	200	90	Permanent				Dramatic relief.
3	30	200	100	24 hours	200	100	Permanent	Relief within 2 minutes of injection.
4	27	200	85	Permanent				Relief within 1 minute of injection.
5	21	200	90	do				Severe pain with apprehension.
6	56	200	40	30 minutes	[3] NR			Dramatic relief.
7	23	200	40	do	200	90	Permanent.	
8	33	[1] 200	[2] 85	Permanent				
9	29	200	0		NR			
10	36	200	40	Permanent				
11	58	75	60		NR			Within 30 minutes obtained 100 percent permanent relief.
12	44	200	95	Permanent				
13	22	200	100	30 minutes	200	70	Permanent.	
14	49	200	65	Permanent				
15	21	200	75	5 minutes	NR			Second dose not required because cycle of pain and breathholding was interrupted.
16	20	200	100	Permanent				
17	21	200	50	do				
18	21	200	75	do				
19	49	200	95	do				
20	31	200	75	do				
21	36	200	50	1 hour	200	40	2 hours	Third dose of 200 mg. gave 50 percent permanent relief.
22	28	200	50	3 hours	200	50	Permanent.	
23	28	200	75	Permanent				
24	27	200	50	5 minutes	NR			Second dose not required because cycle of pain and breathholding was interrupted.
25	34	200	90	Permanent				
26	21	175	60	do				
27	43	200	75	do				
28	32	200	90	5 hours	200	70	Permanent.	

[1] Given prophylactically 10 minutes prior to biopsy.
[2] Estimated percent less pain than on previous biopsy.
[3] NR—Not repeated.

which was permanent. The patient to whom the drug was given prophylactically had considerable pleuritic right shoulder and abdominal pain following a previous removal of a specimen for liver biopsy. He was given no preoperative medication except 200 mg. of tetraethylammonium chloride intravenously 10 minutes prior to the procedure. His preparation consisted only of infiltration of the skin at the needle insertion site with 1 percent procaine. No procaine was used in the subcutaneous tissues, the pleura, or the liver capsule. The only complaint was a dull midabdominal pain during the procedure and later only mild abdominal pains lasting about 2 hours. Since it is common to note such moderate pain without the use of a special medication, the exact role of the drug in preventing pain in this patient is inconclusive. Only one patient of this series obtained no relief.

The effectiveness of this drug is not limited to the extent of relief experienced by the patient nor to the permanence of the relief. With the onset of the sharp, shooting pain of induced pleuritis, the patient immobilizes his chest and holds his breath in an attempt to alleviate his discomfort. At some point, however, he must inspire and with this he again feels pain. The relief from this type of pain with tetraethylammonium chloride is rapid and dramatic. It often occurs within 1 minute of the time of injection. The patient is then able to inspire with minimal or no pain. Thus the cycle of pain followed by breathholding is stopped and the patient can regulate his breathing with no discomfort.

DISCUSSION

The use of tetraethylammonium chloride to relieve pain was described by Caller et al. (*4*). Visceral and anginal pain have also been alleviated with this drug (*5*). Other than the experience recorded by Israel et al. (*3*), we are not aware of any reports of the relief of pleuritic pain with tetraethylammonium chloride. In our series the pain alleviated has been mainly in the pleura and right shoulder. Little effect has been noted on the dull abdominal discomfort produced by the procedure. This drug was immediately effective in relieving the nausea in four patients. This is probably related to the reduction of gastric motility by tetraethylammonium chloride (*6*). In our series we have noted no adverse effects from this drug. The dose used has been well below the levels at which toxic manifestations are recorded (*7*). This, plus the fact that most patients in this series were not over 40 years of age, may account for the absence of complications. The toxic manifestations and contra-indications of this drug have been described by Birchall et al. (*8*) and should not be disregarded particularly if there is any evidence of excessive bleeding. It is not intended that the drug should be used routinely, but rather

that it should be reserved for the patient with distressing symptoms following removal of a specimen for liver biopsy.

SUMMARY

The intravenous administration of 200 mg. of tetraethylammonium chloride gave relief of pain following removal of a specimen for liver biopsy in 26 of 27 patients. Suggestive evidence is given for the prevention of pain with the use of the drug prophylactically in 1 patient. Tetraethylammonium chloride would seem to be a desirable drug to use for this purpose because of the dramatic relief from pain and nausea and because of its lack of side effects.

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Recurrent Ectopic Pregnancy

Report of a Case

JOHN LINGENFELDER, *Lieutenant (MC) U. S. N.*[1]

RECURRENT ectopic pregnancies are unusual and occur in about 4 or 5 percent (*1*) (*2*) of cases in women who are able to conceive following operation for that condition. Recurrent ectopic pregnancy in the site of a previous salpingo-oöphorectomy for tubal pregnancy is, however, exceedingly rare. A survey of the available literature discloses 37 previous cases of this unusual and interesting condition. In 1926 Hasselblatt (*3*) made an exhaustive survey and was able to report 19 previous cases and added 2 cases. In 1935 Deutsch and Clahr (*4*) found 8 other case reports in the literature and reported a new case of their own. Since that time Bartlett (*5*), Casler (*6*), Forman (*7*), Ballentyne et al. (*8*), Gee (*9*), and Frankel (*10*) have all reported additional cases.

CASE REPORT

M. R. N., a 30-year-old white gravida III, para I, was admitted on 13 June 1947. Her chief complaints were cramps in the left lower quadrant of the abdomen for 3 days and weakness and fainting during the preceding 12 hours. The initial onset of symptoms had followed coitus. Her previous history included a left salpingo-oöphorectomy in 1939 for ruptured left ectopic pregnancy. At this time the surgeon also performed a right salpingostomy and uterine suspension. In 1942 another uterine suspension was performed and the following year in 1943 the patient had a spontaneous 3-month abortion. In October 1946 the patient had a full-term normal delivery of a viable male infant.

She stated that her last menstrual period occurred on 6 May 1947 and was normal in character and flow. After the onset of her first symptoms she consulted a physician who shortly before entry into the hospital performed a pelvic examination which brought on an acute exacerbation of pain and faintness. She was then transferred to the hospital with a presumptive diagnosis of ruptured ectopic pregnancy. Upon admission, she was in obvious distress and in early shock; blood pressure was 96/66 and the pulse rate was 112. Examination at that time revealed tenderness and muscle guarding in both lower quadrants, more severe on the left. On pelvic examination an indefinite but extremely tender mass in the left adnexal region was felt. The cervix was softened and slightly cyanotic. A cul-de-sac aspiration revealed bright red blood. Plasma infusion was begun prior to the cross-matching for transfusion. A diagnosis of ruptured ectopic pregnancy was believed certain.

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Operation.—Gross blood and clots were noted on opening the peritoneum. The left uterine cornu was seen bleeding briskly from what appeared to be a ruptured pea-sized bleb at the apparent site of the previously excised tube. This entire area was removed with a cuneiform excision and the defect of the uterus was closed with interrupted chromic catgut sutures. Inspection of the right tube and ovary showed normal-appearing organs. The abdomen was closed in layers. Transfusion of 500 cc. of citrated whole blood was started just prior to completion of surgery, at which time the patient had received 700 cc. of plasma. The patient's condition was much improved following surgery. Her postoperative course was uneventful.

Pathologist's report

Gross examination.—Specimen consists of a wedge-shaped piece of tissue measuring 0.75×1.5×1.5 cm. On one aspect there is a bleblike cyst measuring 0.5 cm. in diameter and which is apparently ruptured. The cyst has a hemorrhagic appearance.

Microscopic examination.—The section reveals smooth uterine muscle invaded in areas by hyperchromatic syncytial cells. There is also an area of hemorrhage with chorionic villi within it. These villi have two layers of cells. Within the myometrial portion of the section there is a cavity lined by cuboidal epithelium resembling the epithelial lining of the interstitial part of the uterus.

Diagnosis.—Ectopic pregnancy in stump of previously excised left fallopian tube.

DISCUSSION

There are several interesting aspects to this case aside from the rarity of the condition itself. First, interstitial ectopic pregnancies usually progress to a much later stage of development before rupture occurs and in this case, as in Richardson's (*11*) case, one must postulate that implantation occurred in the most superficial part of the remaining portion of the tube for rupture to occur so early. Another interesting point is that the patient had had two subsequent pregnancies after the first salpingo-oöphorectomy for tubal pregnancy, and this would indicate that the remaining right tube was patent. The patient did not give the usual history of preceding sterility for several years; her last pregnancy had terminated only 8 months before with a full-term normal delivery.

Since only the right ovary remained at the time of this accident, it is evident that a transmigration of the ovum occurred with implantation in the opposite tube. As to the mode of transmigration there are three possibilities:

(*a*) Internal migration of an ovum which had been fertilized in the right tube, across the fundus and then up into the partially or completely canalized cornu on the left side.

(*b*) External migration of the ovum and implantation in a pocket of the tube on the left side, which had regenerated or recanalized and through which sperm had migrated to fertilize the ovum prior to nidation.

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(*c*) External migration of an ovum which was fertilized by spermatozoa which had ascended through patent right tube with nidation occurring in a pocket of the tube at the site of the previous operation.

The first explanation in this case would seem to be the easiest mechanically, and there is some evidence (Forman (*7*)) to indicate internal migration can occur. Most writers (*4*) (*11*) (*12*) believe external migration to be the usual method of implantation, and this cannot be ruled out in this case.

The treatment in this case was cornual excision which would theoretically offer the most assurance against recurrence. A wedge excision in all salpingectomies would seem to be indicated if not offering too many technical difficulties at operation. While cornual excision is probably the surest method of preventing recurrence, there are instances in which this has failed (Nache (*13*) quoted by Ballentyne et al. (*8*)). Labry (*14*) in discussing LeClerc's (*15*) paper stated that he believes that occasionally in tubal abortion the tube may be tamponaded after expression of the pregnancy and the tube then left in situ. In the same paper Cotte (*16*) expresses the opinion that the corresponding ovary should be removed with the pregnant tube in order to insure that ova dropped from that side would not be wasted by being unused. The latter would appear to be an extreme viewpoint in that it is known that external transmigration can occur; further ovarian tissue should be conserved. The view of conserving the tube in tubal abortion would seem to entail immediate as well as future hazard from recurrence and from a practical viewpoint can seldom even be considered.

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Thrombocytopenic Purpura

Discussion and Report of a Case

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THE tendency to bleed into the skin and from the mucous membranes is known as "purpura." As a term it has "no more pathological significance than has the term, anemia" (*1*).

Any classification of hemorrhagic diseases is unsatisfactory because of our incomplete knowledge of the fundamental processes involved, but, in general, three main types may be distinguished: (*a*) those associated with a disturbance in one or more of the chemical factors involved in clotting; (*b*) those resulting from deficiency or defect of the blood platelets; and (*c*) those secondary to an alteration in the capillary walls.

ETIOLOGY

Many theories have been advanced concerning the cause of thrombocytopenia (*3*). Kaznelson believed that the platelets were destroyed in the spleen in excessive numbers, and more rapidly than normal. Frank postulated that a substance is formed in the spleen which inhibits platelet formation from the megakaryocytes. It is possible that the primary disorder is a defect in the capillaries, permitting blood to escape through their walls. According to this view, the platelets are used up in attempt to close up the multiple vascular defects.

The importance of a capillary defect as a factor in the etiology of purpura is indicated by clinical experience. As pointed out by Wintrobe (*3*), hemorrhage is not always closely correlated with the degree of thrombocytopenia and purpura does develop when capillaries are deliberately damaged, as in the tourniquet test.

Thrombocytopenic purpura may be either primary or secondary. The latter is by far the more common (*3*). It may be caused by infections, either current or recent, by drug intoxications, or by a disease causing depression of the bone marrow (*3*).

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Primary thrombocytopenic purpura rarely occurs in more than one member of a family, although a family history of bleeding tendency is not unusual (*4*). Women are affected more often than men, young children more often than older children, and Negroes uncommonly (*4*). A predisposition to allergic manifestations, especially asthma, has been noted in some patients (*5*).

DIAGNOSIS

The usual duration of this disease is from 3 to 18 months (*6*). A slightly enlarged spleen is palpated in about one-third of the cases; general lymph node enlargement is not found (*3*). This is the most common form of the disease. There are two other forms (*7*); the first, and most serious, although fortunately the rarest, is the fulminating form; the first attack may prove fatal, and hemorrhage may be widespread. In addition to the visible bleeding, the patient may have hidden hemorrhage and the central nervous system may be involved. Abdominal pain may accompany gastrointestinal bleeding. The other, a chronic, recurrent form, is characterized by periodic episodes of hemorrhage of varying severity, with intervals of apparently perfect health during which the bleeding tendency lessens although the platelet count remains about the same low level.

Thrombocytopenia may occur with or without noticeable symptoms of free bleeding, or even of prolongation of the bleeding time. Spontaneous bleeding usually does not occur unless the platelet count is below 60,000 cu. mm. (*3*).

Primary thrombocytopenic purpura is diagnosed as such only by exclusion of all the known underlying causes for platelet deficiency. With increasing skill and further investigation, the diagnosis of primary thrombocytopenic purpura becomes less common.

The hemostatic properties of the platelets are well known. By their agglutinative properties they can form a plug which serves directly to seal an injured blood vessel until a permanent clot is produced. Upon their subsequent dissolution a substance is released which may initiate the coagulation process. Only a small number of platelets are required for this. The excess not used brings about retraction of the clot, known as syneresis, by some mechanism not known at present. Syneresis is important in hemostasis because it causes the blood vessel walls to come together. When there is no platelet excess, blood clotted in a test tube fails to retract.

Capillary resistance may be measured by the tourniquet test. By compressing the arm or leg with a sphygmomanometer cuff midway between the systolic and diastolic levels for 5 minutes, petechiae may be made to appear below the point of compression in numbers proportional to the fragility of the capillaries. A more informative test

is the suction test, in which suction is applied on the forearm and the negative pressure recorded at which petechiae appear. Normally this ranges between –200 and –300 mm. of mercury (*2*).

In children, great difficulty is encountered in differentiating this condition from leukopenic leukemia, for thrombocytopenic purpura is almost invariably present, and is often the first indication of leukemia (*6*). Bone marrow biopsies are helpful in eliminating this diagnosis.

TREATMENT

The natural tendency in acute phases or exacerbations of idiopathic thrombocytopenic purpura is toward improvement (*3*). Treatment, therefore, should consist of bed rest, general nursing care, appropriate diet, and antianemic treatment. There is no evidence that any of the vitamins are of specific value (*7*). If there has been much bleeding and shock is imminent, blood transfusions are necessary. Small transfusions at intervals of 2 to 7 days have been said to stimulate blood formation and to supply platelets (*3*).

The popular conception that splenectomy is an infallible remedy can be challenged because the varied course of the disease makes adequate appraisal of the effects of surgery practically impossible. There are, however, indications for surgery, such as severe bleeding which fails to subside after repeated transfusion, frequent recurrences which jeopardize growth or development or the social or economic status of the patient, the occurrence of the disease in women past puberty because of the possibility of serious bleeding at menstruation or during pregnancy (*4*).

CASE REPORT

A 2-year-old white boy was admitted because of petechiae and ecchymoses widely scattered over the cutaneous surface of his body and, to a lesser extent in the mucous membranes. When these appeared, suddenly, 4 days prior to admission, he was otherwise perfectly well except for a mild upper respiratory infection. He had no lymphadenopathy, but the spleen was palpable 3 cm. below the left costal margin. The day following admission he had several moderately severe nosebleeds.

On admission, his bleeding time was 9½ minutes, and no clot retraction occurred after 24 hours. This suggested a thrombocytopenia; confirmed by a platelet count of 45,000 per cu. mm. The clotting time was normal (7 minutes). The tourniquet test was positive. There was no history of allergy. However, while in the hospital he had a contact dermatitis from merthiolate over the site where a specimen of bone marrow was taken for biopsy. His father has seasonal hay fever. His mother has hives when exposed to temperature variations. One brother had an intestinal allergy to milk, both human and bovine, and was raised on a soybean milk substitute the first 2 years of life. One sister has had one attack of asthma.

On the day preceding the onset of his symptoms, this patient had received nose drops containing tyrothricin. He had had no other medications for several months.

Following the epistaxis on the second hospital day, a transfusion of 140 cc. of citrated whole blood was administered. By the next day the bleeding time had dropped to 4½ minutes, and the platelet count rose to 144,000. A second transfusion of 240 cc. was then given, and the bleeding time dropped to 2 minutes. Seventeen days after onset the purpura completely disappeared, and the spleen was barely palpable.

This patient has been observed for 19 months, and has shown no signs of recurrence.

SUMMARY

Thrombocytopenic purpura occurs because of some factor which brings about a reduction of the number of blood platelets. It appears in an acute or chronic form and is characterized by bleeding into the skin, subcutaneous tissues, and internal organs. Spontaneous recovery is the rule and drugs are of no value.

A résumé of the initiating factors, signs, and symptoms, and the treatment of thrombocytopenic purpura is presented.

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Treatment of Bronchial Asthma With Psychotherapy

Report of a Case

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THE relationship between bronchial asthma and allergy has been familiar since the discovery of allergens. It has been found that the person with asthma often is not only sensitive to a specific substance, removal of which exerts a therapeutic effect on the illness, but also that he often presents a history of other allergic manifestations such as eczema, urticaria, or hay fever—a true allergic diathesis. The importance of emotional factors in the causation of asthma has gained acceptance more recently and has followed the work of a small number of investigators, among them Salter, Rogerson, Obendorf, French, Alexander, et al. It had been found that, not unlike the allergic diathesis in asthma, there also seems to be a rather typical emotional diathesis—a constellation of environmental and psychologic characteristics that are seen with great frequency in the asthmatic.

The patient is usually described as a passive-aggressive-dependent type of person whose love and dependency needs are so great as almost to defy fulfillment. A sense of insecurity and tremendous amounts of unconscious hostility and latent aggressive trends result from these relatively unfulfilled dependent needs. The principal parent figure, usually the mother, is found to be an aggressive domineering person whose erratic, smothering type of protective love cloaks her own feelings of hostility and her frustrated achievement drives. The result is usually a timid, querulous person with few inner strengths, and severely impaired ability to function as an independent organism. Weiss has compared the asthmatic wheeze to the cry of the infant for his mother.

The following case is presented as an illustration of a situation in which both allergic and emotional factors were operative in the causa-

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tion of the patient's asthma. It is of additional interest insofar as it presents a longitudinal picture of diagnostic and treatment procedures at the Child Guidance Clinic of the Neuropsychiatric Service at this hospital.

CASE REPORT

This 10-year-old boy was first brought to the clinic because of severe bronchial asthma in September 1948. The mother complained also of the boy's irritable, seclusive, and occasionally bizarre behavior. He spent most of his time sitting in his rocking chair listening to the radio; he spoke infrequently, used sign language a good deal, and showed much negativistic behavior toward his parents. His attendance at school was erratic because of his numerous asthmatic attacks in the past 8 years. At the time of his coming to the clinic, the mother estimated that the patient was spending from one-half to two-thirds of his time in the children's ward of the hospital. Although his asthmatic attacks while in the hospital were neither as severe nor as frequent as when he was at home, vigorous medication was still necessary when he had his attacks. In the first year and a half of his life the patient had eczema and urticaria although there was no history of allergic phenomena in the family. Thorough examination had revealed no significant pathologic findings, and the child had been referred to the Child Guidance Clinic for further study.

He was a wanted child and was born about 20 months after his parents' marriage. When he was 4 years old his father left for active duty in the Air Force and did not return home until the patient was 6. During that time the patient and his mother were inseparable and the return of the father into the home precipitated repeated emotional storms in one of which the patient cried to his mother, "Let's lock the door and not let him in." Relationship between the boy and his father improved somewhat in the past 3 years but there were no open demonstrations of affection. The birth of a baby sister when the patient was 7 produced no obvious disturbance. The mother always felt that the boy was sickly, abnormal, and "slow," and had taken him to a great number of physicians. She was incensed by his continuing passively hostile attitude and his inability to make a better showing in school. His asthmatic attacks frequently came on in the evening shortly before the mother's own bedtime. When this happened, the mother was obliged to spend the night in her son's room. An interview with the father was considered desirable, but he could not leave his job during working hours.

Examination

The patient was a small asthenic, rather elfin-looking boy, appearing somewhat younger than his stated age. He insisted on remaining with his mother while she was interviewed by the psychiatrist. He said he would not listen, but it was noted that the comic book that he was supposedly reading was held upside down. Questions were answered with single words or by sign language, and for the remainder of the time he sat dreamily in his chair, gazing at the opposite wall of the office. His behavior continually angered his mother who alternately threatened and spurred him on.

Psychologic examinations revealed that the boy was functionally of borderline mentality with a mental age not exceeding the average 7-year-old. His I. Q. (Stanford-Binet) was 70. There were strong suspicions, however, that this was not a true indication of his basic potentialities as emotional blocking might have

played a role in this performance. Part of this opinion was based on the fact that his reading ability was equal to that of the average child starting fourth grade. His comprehension and recall were also adequate and equal to that of the average child 9 or 10 years of age. He appeared to have a well-developed fantasy life and showed many symptoms of personal maladjustment.

Treatment

Both the patient and his mother were given weekly therapeutic interviews; the boy was seen by the psychiatrist in play therapy and the mother by the psychiatric social worker. Because of several severe bouts of asthma, therapy was not started until 3 months after the initial contact with the clinic.

When the patient entered the playroom for the first session he was indecisive and announced that the toys were of no interest to him. After some encouragement he finally decided to play checkers. The first time the patient made a "king" and it was pointed out that he was now a "king on the board," he said, "No, I'm not; I'm nobody." He lost all the games and said, "I don't mind losing. It's just the sportsmanship." It was suggested that it was all right to feel bad about losing or about being unimportant, but the patient could not accept this. His feelings about his smallness were again brought out as he had the therapist build large block structures, followed by the construction of much smaller buildings of his own. The differences in size were further elaborated verbally. In the second session the patient experimented with small shows of hostility, throwing crumpled paper on the floor, messing delicately with the finger paints, and then more enthusiastically when he discovered that rejection was not threatened. As he gained confidence he spattered paint and tore off sheets of paper with distinct enthusiasm and a voluble flow of speech. He came to the third session with his own set of finger paint and produced a picture of a heart inside a larger heart, writing the word "love" under it. He asked for the therapist's first name and then wrote "Arne's" above the heart. This meant "Arne's love" which the therapist obviously owed to his wife. In the patient's home, however, there was no love since his mother and father always fought. He disregarded the suggestion that love seemed rather important to him and produced another version of "Arne's love." He then admitted that he was not loved, said that love was what he wanted, and volunteered to produce something for every room in the Child Guidance Clinic. He said there were five members in his family including a talking parrot, but specifically excluded the younger sister, stating that he was the only child. During the session he appeared to be testing out the therapist, making a bid for his love and attention, and indicating how lonely and unloved he was.

Next time the patient brought the therapist an orange. He then spent most of the time drawing animals for the therapist and adding abdominal appendages which he first called "the tail," then later "the tip" and finally "the tits." There was some discussion of masculine-feminine differences, but the patient blocked rather readily. In the next period he further amplified his feelings about his family by drawing a heart with an arrow through it, printing "happy" beneath it. He said this represented the whole world and also his family, both of which he wished to be happy. He then drove a toy rubber knife through the heart until he had torn it up completely, stating that this was what happened when there was a fight in the family. There followed a discussion of how the children of a family felt when the parents fought, and the patient was finally able to admit that aggressive attitudes on the part of the parents severely threatened the security of the children. The patient then carved the initials "USA" on

the back of one of the playroom chairs, and when it was suggested that it would be wise to stop since this would eventually come to the attention of the general, he launched into an attack against "the old general who is always putting his nose into things," which increased in feeling until the patient was running around the room, shaking his fist and swearing. It was suggested that generals might be like fathers and the patient agreed, adding that they were even more like mothers, "always minding somebody else's business." After verbalizing and acting out tremendous amounts of hostility the patient printed a sign reading, "mind your own business," hung it outside the door, then in a triumphant frame of mind made his mother come back to see it.

In the following session the patient became physically aggressive toward the therapist and when it was pointed out that this could not go on, the patient hit himself over the head with his toy revolver. It was suggested to him that he probably often hurt himself when he felt like hurting others. He said this was true, and then described how he wished he were a magician so that when his parents came to whip him, he could turn the tables and give them a merciless drubbing. Unfortunately he was small and unimportant and his wishes never mattered. The therapist agreed that he could not do this, but suggested that it was sometimes as good to talk out one's feelings and the patient agreed.

In the next several interviews, the patient continued to act out aggressive feelings toward the therapist, gradually developing a more realistic conception of the limits to which he could carry this. He could now express his feelings of hostility and frustration over losing checker games and was able to state further that he realized he lost because of his own inexperience compared to the therapist's and that eventually he would get better and might win. He was complimented both on the improvement in his playing technique and on his more realistic and mature attitudes. By the end of the thirteenth session it was felt that the patient deserved a temporary cessation of therapy since improvement had been so great. At that time he had not had an attack of asthma for about 7 weeks.

The mother reported distinct changes in the boy's personality, with enthusiastic socialization, a normal amount of small-boy aggressiveness, and an increasingly happy relationship between father and son. She was also pleased that his work in school had shown improvement. Her own attitude, too, had shown definite changes. She had become relaxed and relatively free of anxiety concerning the patient. She felt that he was capable of proceeding at his own rate and let him do so. The result was obvious improvement in the mother-son relationship. A general change for the better in the family atmosphere had occurred along with symptomatic improvement in the boy.

In an attempt to determine whether there was any noticeable change in the level of mental function and potential over that indicated by the first set of psychometric examinations, a second group of tests was given to the boy 1 month following cessation of therapy. The Stanford-Binet findings were astonishingly consistent in their demonstration of a functional age level 3 years below the stated age. Arithmetical conceptions, practical judgment, visual motor coordination, and language comprehension all continued to show retarded developmental status. On the other hand. the Rorschach data delineated basic intellectual qualities that were well above average and near the adult level. There was good productivity, ability to maintain attention, abstract conceptualization, and adequate intellectual control. The performance intelligence examination (Goodenough) reflected growth in use of abilities during the therapy period. Since school work was also up to average or better in the later stages and following therapy, and his reading also adequate for his grade, these, along with the

Goodenough scale and the Rorschach, seemed to refute the Binet findings of continued borderline intelligence. The psychologist made the suggestion that the possibility of organic dysfunction, especially convulsive disorder should be explored. An electroencephalogram was normal and there was no evidence of any organic lesion. The final impression was that the boy was still emotionally immature for his age and approximately at the intellectual level as indicated by the Binet rather than the Rorschach test.

In the 9 months since the termination of therapy, the patient has been seen periodically. He has been completely asthma-free except for one brief episode early in the pollen season.

DISCUSSION

This patient presented a problem of severe bronchial asthma associated with a moderately severe personality disorder. His asthma appeared directly related to a combination of definite allergic diathesis, plus a disturbed emotional situation in the family environment, manifested primarily by poor parent-child relationships. Over a relatively short period of therapy in which the boy was seen once each week for 13 weeks by the psychiatrist, and the mother for half-hour periods at similar intervals by the psychiatric social worker, definite improvement occurred in family interpersonal relationships as well as in the boy's personality. The complete clinical remission of the patient's asthma, with the exception of one brief episode early in the pollen season, would seem to indicate that psychogenic factors were operating as an important trigger mechanism in setting off this patient's attacks of bronchial asthma.

Treatment of Rhus Dermatitis

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THE appraisal of any form of treatment of *Rhus* dermatitis is made unusually difficult by individual variations in the type of lesion and symptoms observed following exposure. For example, some patients have chiefly papular lesions; others have bleblike, oozing lesions; and some may have little or no itching. The final extent of involvement and ultimate severity of the disease cannot be accurately estimated at first because new lesions often continue to appear 48 to 96 hours after exposure. Furthermore, trauma produced by scratching or rubbing during sleep and the presence of secondary infection further delays recovery. For these reasons, comparisons of results of treatment in different patients are not only valueless but misleading. Furthermore, comparisons of new treatments with treatments used by the same patient on previous occasions are invalid because the degree of dermatitis in the previous attack is not known to the investigator, and patients' memories are unreliable. Successive, not simultaneous, use of two or more medications cannot lead to valid conclusions because the first medicament is usually applied while the disease process is in ascendency, whereas later treatments may merely coincide with spontaneous recovery. Finally, unless patients are carefully observed in a hospital one is uncertain whether the remedies prescribed are properly used.

Textbooks on dermatology mention many remedies for the treatment of *Rhus* dermatitis but there is no convincing evidence that any of them possess superior merit. The mere presence of many recommended forms of treatment usually indicates that treatment is unsatisfactory.

A review of the literature reveals inconsistent statements, unproved opinions, and uncritical conclusions regarding the prophylaxis, treatment, and duration of *Rhus* dermatitis. For example, Alderson (*1*), Bivings (*2*), and Caulfield (*3*) recommended using extracts of *Rhus toxicodendron* in treatment but used no control cases, whereas Howell (*4*) using control patients, clearly showed that there was no significant

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difference in the rate of healing between injected and noninjected groups. He stated that the fundamental basis for treatment with intramuscular injections of poison ivy extract was unsound. Sharlit and Newman (*5*) treated 74 patients with an effective extract of poison ivy, and gave 8 control subjects injections of absolute alcohol. Although they concluded that their extract was curative in *Rhus* dermatitis, they also stated that slight variations in the technique of preparing an extract meant the difference between a therapeutically effective product and a useless one.

From our observations covering 4 years, we believe that differences in statements regarding the duration of the disease are explained by differences in plants, intensity, location, and duration of exposure to the offending plant, and differences in individual hypersensitivity and reaction. The importance of intensity and duration of exposure was dramatically demonstrated by Molitch and Poliakoff (*6*), who stated that patients inoculated with poison ivy extract remained free of the disease despite playing in an environment containing poison ivy, but incurred severe dermatitis when they held plants for 30 seconds.

Witherspoon (*7*) advocated the use of a cream containing 1 percent menthol or phenol and 10 percent sodium perborate, but no controls were used. Of 70 patients, 90 percent were clinically cured in 5 to 7 days, but in none was the disease severe enough to warrant hospitalization. Results of treatment of hospitalized patients with severe involvement were not stated although such patients received similar treatment. Blumenthal and Rosenberg (*8*) reported relief from pruritus in 12 of 14 patients treated with 50 mg. of benadryl ever 4 to 6 hours but did not describe the severity of the disease. Tweedall and O'Connor (*9*) gave 100 gm. of pyribenzamine orally 1 hour before applying an extract of *Rhus toxicodendron* to 5 persons who had strongly positive patch tests for this substance, and 50 mg. at the time of application, as well as every 4 hours for 24 hours. They observed only moderate relief from burning and itching and no prevention of dermatitis. Furthermore, the senior author in 1946 used benadryl orally, in cases of *Rhus* dermatitis, in doses identical to those used by Blumenthal and Rosenberg without affecting the pruritus.

Robinson (*10*) sprayed the lesions in 101 patients daily with ethyl chloride. Although no controls were used, and there was no separation of patients by degree of severity, he believed that recovery was accelerated inasmuch as patients with large bullae recovered after a week of treatment, whereas in our experience such patients rarely recovered in less than 15 days. However, Robinson did not state the duration of illness prior to the start of treatment. The efficacy of this form of treatment has not been confirmed by other investigators.

Sulzberger, Baer, and Levine (*11*) used pyribenzamine ointment locally for various skin disorders but not for *Rhus* dermatitis and reported that it produced an eczematous allergic reaction in 2 of 90 patients. Strauss (*12*) confirmed this observation and showed that pyribenzamine, not the vehicle for the drug, produced an acute, oozing, edematous dermatitis.

Using a large number of hospitalized patients of the same age group, the results obtained by the simultaneous local use, in the same persons, of 2 percent pyribenzamine ointment and calamine lotion containing 1 percent menthol and 1 percent phenol were compared. In addition, the effect of orally administered pyribenzamine was observed in 5 patients. These results are shown in table 1. As far as possible, areas of about equal involvement were chosen on each upper or lower extremity, treated differently, and compared daily. In addition all areas were treated with warm compresses or warm baths. All patients were examined daily and were invited to comment at the termination of treatment.

TABLE 1.—*Comparison of effects of pyribenzamine ointment and calamine lotion with phenol and menthol.*

	Grade of severity of dermatitis [1]					
	I	II	III	IV	V	Total
Patients	9	19	30	11	1	70
Pruritus severe	9	18	26	10	1	64
Pyribenzamine more effective for pruritus	0	6	12	4	1	23
Calamine more effective for pruritus	4	8	8	3	0	23
Pyribenzamine and calamine equally effective for pruritus	5	4	6	3	0	18
Healing faster with pyribenzamine	2	6	13	3	1	25
Healing faster with calamine	0	4	3	3	0	10
Healing equally fast	7	9	14	5	0	35
Patient preferred pyribenzamine	2	8	17	5	1	33
Patient preferred calamine	4	8	8	3	0	23
Patient had no preference	3	3	5	3	0	14

[1] Grade I least and Grade IV most severe.

In three patients calamine caused excessive drying and cracking of skin, especially around joints. On the other hand, three patients treated with pyribenzamine ointment had urticaria (two generally and one locally). The symptoms of urticaria were quickly and completely controlled by the use of an antihistaminic, tagathen, given in doses of 50 mg. four times daily. In four patients, pyribenzamine ointment, although helpful up to a point, seemed to produce redness and burning sensations and to retard complete recovery. When its use in these patients was discontinued and succeeded by nupercainal, relief from the burning sensation and complete recovery promptly occurred. In joint regions pyribenzamine ointment kept the skin soft. The masking effect of calamine lotion had a psychic appeal for some patients. A few patients commented favorably on the retarding of serous oozing by the calamine lotion, but most thought that greater

oozing with the pyribenzamine ointment produced more rapid decrease in swelling.

Fifty milligrams of pyribenzamine was given orally five times a day to four Grade II patients, but was promptly discontinued because it did not relieve itching. Two patients had a complicating purulent infection that responded dramatically to use of aureomycin orally. In general, removal of the tops of the larger blebs and the application of warm compresses appeared to lessen pain and accelerate healing. Unopened small blebs and vesicles dried readily.

COMMENT

Appraisal of the effects of various forms of treatment for *Rhus* dermatitis is difficult because of uncontrollable variables. Using different forms of local therapy in areas of a similar degree of involvement, in the same patient, allows the observer to evaluate the relative merits of the treatments employed. Unless investigations are conducted in this manner, conclusions are likely to be invalid. Contradictory statements concerning the efficacy of intramuscular injections of poison ivy extract in the treatment of *Rhus* dermatitis result from the fact that lesions on the same patient cannot serve as a basis of comparison. Unfortunately, most workers have used few if any controls. It is recommended that a large group of hospitalized patients be used for an appraisal of the effect of injections. Equal numbers of cases of about equal severity should be chosen for the treated and the control groups. The patients receiving injections should receive no local treatment. The opening of the larger blebs and bullae and the application of warm Burow's solution compresses is an effective method of treating *Rhus* dermatitis. Although it is uncertain whether the additional use of medicaments applied to the surface essentially shortens the course of the illness, this investigation gave some indication that the use of pyribenzamine ointment, locally, may accelerate healing.

SUMMARY

Rhus dermatitis constitutes an important cause of loss of time from duty. In 70 patients, results of the simultaneous use of pyribenzamine ointment and calamine with phenol and menthol were compared. These treatments were about equally effective in the control of pruritus. No constant effect on the speed of healing was observed since one-half of the patients improved equally rapidly with both medications. Of the remaining half, 71 percent improved more rapidly with pyribenzamine. Further trials with pyribenzamine ointment locally are recommended, especially on lesions around joints.

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THE PROGNOSIS IN JAPANESE B ENCEPHALITIS, by Charles D. Aring, M. D. Archives of Neurology and Psychiatry **62**: 757–765, Dec. 1949.

Japanese B encephalitis resembles other severe infections of the central nervous system in that it may produce residual neurologic effects. There is, however, a chance for slow amelioration of symptoms because of the great compensatory powers of nervous tissue, one area substituting for another. If crippling neurologic signs do not appear in the first 10 days, the patient will almost surely go on to recovery. The only exception to this is the possible development of Parkinsonism. More than a single area of gray matter is involved in Japanese B encephalitis, and the substantia nigra is among them. To attribute the emotional disturbances that have been observed following Japanese B encephalitis to that infection would be to perpetuate a medical error that has been made too frequently in the past. Men should not be expected to be any more emotionally mature following an acute infection than they were prior to it. All the evidence so far collected indicates that, at most, an acute illness may predispose to neurosis in an already unstable person. The majority of the American patients who had Japanese B encephalitis were unusually concerned about what might happen to them. Uncertainty on the part of medical personnel was transmitted to the patients, and prolonged hospitalization further contributed to their uneasiness. With psychotherapeutics in mind, it should be possible at this late date and indeed on or about the tenth day of the disease to reassure these patients about their eventual health.—*Abstract.*

Prosthetic Restoration in Gross Malocclusion

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A 24-YEAR-OLD woman reported to the dental clinic with an Angle's Class II malocclusion, severe. She complained of pain in the anterior superior palatine region and pain in the temporomandibular joint, progressive loosening and outward fanning of the upper anterior teeth, inability to incise foods, and progressive oral disfigurement (figs. 1 and 2). She had formed a habit of covering her mouth with a handkerchief or her hand whenever she spoke and would avert her head in an effort to conceal her mouth. The lower anterior teeth were in contact with the maxillary tissue overlying the anterior palatine foramen. There was a gingivitis around the upper and lower anterior teeth. The posterior teeth were well formed and of good calcification but of low eruption, with the greatest occlusal-gingival distance being 5 mm. The lower lip was being pushed downward and forward by the upper anterior teeth. Clinical examination revealed an overjet of 11 mm. with a diastema in the central region and in the cuspid-first bicuspid area. In full protrusion, the lower anterior teeth failed to contact the incisal edges of the upper anterior teeth by 5 mm.

Articulated study models were prepared. Trial removal of teeth and alveolectomy was performed. It was decided that all anterior upper teeth (cuspid to cuspid) should be removed, the frenum cut, and that the lower two-thirds of the labial plate and interproximal bone to a depth of 5 mm. at the gingival crest should be removed. Though incisal space was needed, the lingual alveolar crest was to be filed smooth but otherwise not touched, since such space could be gained by opening the bite. The operation was performed under local anesthesia. The mouth was allowed to heal for 1 month and another model was made. It was not thought feasible to treat this as an immediate case because of the amount of operating involved in such a radical alveolectomy.

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Figure 1.

Figure 2.

Roach type clasps were chosen to retain the case because of the short crowns, but since the contours of the teeth were unfavorable for good retention even by this type of clasp, mild grooves were cut just below the height of the contour on the upper and lower first and second bicuspids and first molars with diamond stones, and smoothed with cuttlefish disks, then pumice, and finally burnished with rubber wheels. These grooves were then treated with 4 applications of sodium fluoride. The grooves were not cut through the enamel, but merely provided

Figure 3.

Figure 4.

definite areas in which to place the Roach T. The bite opening was determined by experimentation to be about 2 mm. This was the least amount that would provide sufficient space for a restoration, and apparently the maximum amount that would still allow for a comfortable freeway space. A trial setup with facings showed that even with the alveolectomy and the new lingual position of the labial portion, it would require 8 teeth to provide a cosmetic result. A lower partial denture with cast occlusal shims would be used to provide the bite opening. The cases were waxed accordingly and cast in vitallium.

The cosmetic result on placement of the dentures is apparent in figures 3 and 4. Closing of the bite caused constant temporomandibular pain varying in intensity in direct ratio to the amount of work performed by the jaw. Within 1 week after insertion of the cases, lessening of this pain was reported, and at the end of 1 month no discomfort was present. At the end of 12 months, there was no recurrence of joint pain. Ability to bite and masticate food with ease without associated palatine pain was reported within 1 week. Psychologically, an appreciable benefit was noticed in about 3 weeks, which was the period necessary for the patient to realize that her mouth need not be covered in conversation, smiling, or laughing. When the moment was reached, the automatic covering gesture with the handkerchief or hand began to cease, and by the end of 8 weeks, had been completely abandoned.

Effectiveness of Newer Drugs in Seasickness

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MOTION sickness has been observed for centuries, but no intensive study had been carried out until World War II when, because of the large-scale amphibious operations and the great number of men needed for sea duty, it was realized that efforts must be made to keep motion sickness at a minimum and thus maintain men at their maximum efficiency.

The data in this article were obtained during a tour of duty on a naval transport, the U. S. S. *General George M. Randall*, which carries dependents, civil service personnel, and troops to installations in the Pacific area. Thus results were compiled from the action of antihistaminic drugs in men, women, and children, giving a more complete picture than would be possible if only young men were used in the study.

Cecil (*7*) defines motion sickness as "a condition due to frequently repeated oscillating movements of the body in a ship or airplane, characterized by dizziness, nausea, vomiting, pallor, and sweating." The syndrome is essentially due to disturbed vestibular function. Visual, psychogenic, and kinesthetic factors play subsidiary roles that vary with the individual. It was found that aboard ship food odors and poor ventilation were predisposing factors.

Symptoms of motion sickness appear suddenly and any or all of the following are present: nausea, excessive salivation, mental depression, vomiting, headache, pallor, and cold sweats. In about 48 percent of persons making their first ocean voyage the self-descriptive condition "epigastric awareness," is present although they do not become ill.

The psychogenic factor has been noted to be an etiologic agent in motion sickness. Desnoes (*5*) pointed out that in some susceptible persons, signs of seasickness develop as they board the ship and prior

[1] U. S. S. *General George M. Randall.*

to sailing. The author has seen three women, who had been seasick on a previous voyage, who became nauseated and vomited while walking up the gangplank to the ship.

According to reports in the literature, infants under 3 years of age and elderly persons are seldom afflicted with motion sickness. It is difficult to determine if the frequent gastrointestinal upsets seen in small infants are due to motion sickness or to the change in milk and water.

Motion sickness in the past has been treated by sedation and/or the use of drugs that suppress the parasympathetic nervous system. Some of the drugs used were sodium amytal, scopolamine hydrobromide, barbital, sodium nitrate, bromides, belladonna, and various coal tar derivatives. Hamilton (*6*), in 1932, reported 400 cases of seasickness in persons between the ages of 16 and 60 years and concluded the most satisfactory drugs in treatment were sodium amytal, scopolamine hydrobromide, and barbital. Bryan reported a series of cases treated by hypnosis with unsatisfactory results.

During World War II, intensive and thorough investigation in the study of motion sickness was carried out. As a result of this work, Army Motion Sickness Preventive, or M. S. P., was conceived. This consisted of the following drugs in a capsule: sodium amytal, 130 mg.; atropine sulfate, 0.3 mg.; and hyoscine hydrobromide, 0.4 mg. This medication was distributed to service personnel (during the war) and was taken one-half hour before embarking and then not oftener than every 4 hours for as short a period as possible. Several investigators reported on the efficacy of M. S. P. as a preventive and there was a wide range of results. The best results reported showed that only 4 percent of personnel became seasick while taking M. S. P. whereas 10.1 percent of those who received placebos and 28.4 percent of the untreated personnel became ill.

Assuming that M. S. P. was the best known method of therapy at that time (1944), it was the only standard that could be used for comparison with newer drugs. I chose benadryl for intensive trial in the treatment of motion sickness because it was suggested to me by another physician who stated that he had no real basis for believing it to be of value but would like to see it tried. About 6 weeks after this investigation was started, Gay and Carliner (*9*) released their work on dramamine. As dramamine is also an antihistaminic and has a benadryl base I was encouraged to continue with the study of benadryl and also secured enough dramamine to include it in the investigation.

The results of the use of these drugs in seasickness only are discussed in this article; I had no opportunity to study their action in airsickness.

PROCEDURE

The medications used in this study were Army Motion Sickness Preventive, benadryl, dramamine, and placebos.

Because different weather conditions were encountered on each trip, all drugs were used in a selected number of cases on each voyage and the results tabulated on a comparable basis. This article is based on the over-all average results during each trip; thus the results obtained from the use of any one drug were not bettered by good weather conditions.

The investigation was divided into two phases: therapeutic and prophylactic.

In the determination of the therapeutic value of the drugs, no presailing medication was given to any passenger. Therapy was begun only when the person reported to sick bay with symptoms of motion sickness. The first four persons seen were given placebo, M. S. P., benadryl, and dramamine respectively in that order, and the routine repeated with each succeeding four persons. Each person was instructed to take one tablet immediately and one every 4 hours thereafter until symptoms were relieved or until five tablets were taken. Those persons given benadryl were told to take two capsules immediately and then one capsule every 4 hours. All were told to return when both objective and subjective symptoms subsided, and the patient's word was used as the index of the effectiveness of the medications. Two days was set as the time limit in which drugs were credited as being of value because in that time 40 percent of those persons under study were symptom-free and required no medication. One thousand two hundred cases of motion sickness were observed in this phase of the investigation.

The prophylaxis of motion sickness was attempted by issuing medication for the passenger, with typewritten instructions to take one capsule 30 minutes before sailing time and then one every 4 hours until the five units of medication given each passenger were consumed. These instructions were repeated verbally to an assembly of all passengers with the added request that they report to sick bay if any illness developed. One thousand six hundred persons were observed in this phase of the study.

RESULTS

Therapeutic effectiveness.—As shown in figure 1, those persons to whom no medication was given remained ill for the first 24 hours; by the end of 48 hours about 40 percent had recovered.

When a placebo (lactose) was given, 14 percent of the persons reported they had recovered at the end of 30 minutes and 46 percent

reported themselves cured in 4 hours when the second placebo was given.

Army Motion Sickness Preventive produced alleviation of symptoms in 17 percent at the end of 30 minutes and maintained a slow but steady rise until, at the end of the second day, 71 percent of the persons receiving the drug reported themselves to be symptom-free.

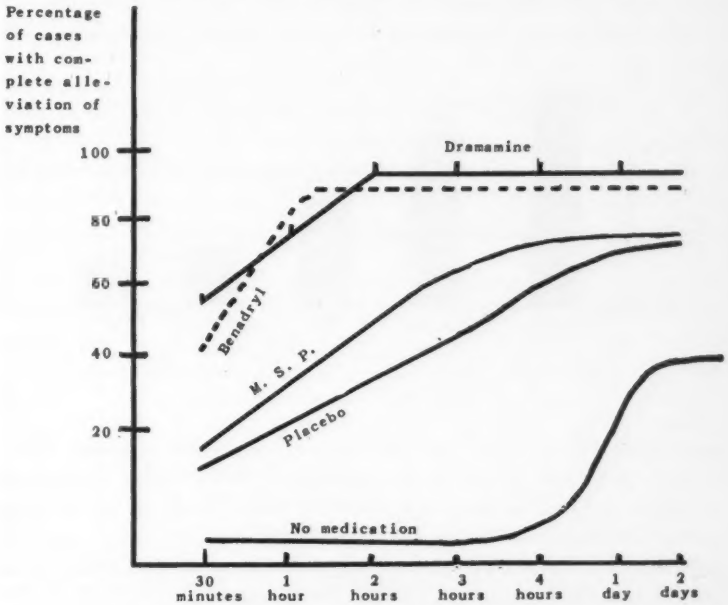
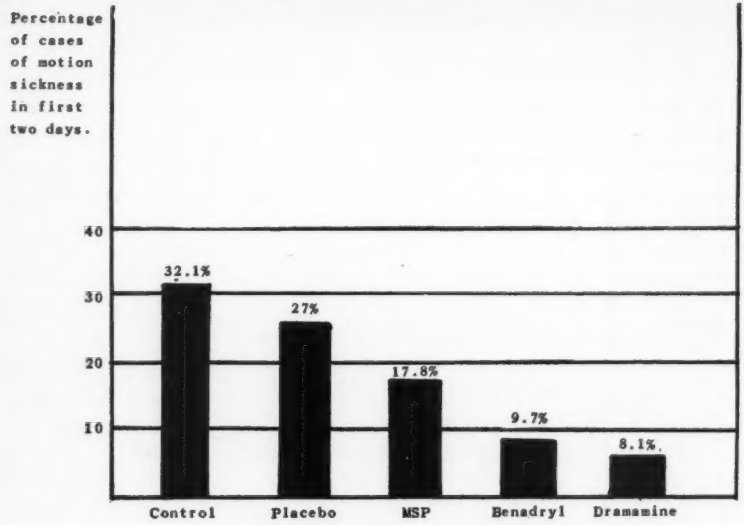


Figure 1.—Effectiveness of therapeutic medication.

Forty percent of those persons receiving 100 mg. benadryl stated that they were "cured" in 30 minutes whereas, at the end of 60 minutes, 82 percent were symptom-free. This increased to 88 percent at the end of 2 hours and no higher percentage of relief was obtained throughout the 2-day period of administration of benadryl.

Dramamine gave relief in 58 percent of motion sickness cases in the first 30 minutes, 76 percent in 60 minutes, and 91 percent in 2 hours. The figure of 91 percent was not exceeded during the 2 days of medication.

Prophylactic effectiveness.—Figure 2 shows that when no medication was given prior to or immediately after sailing, 32.1 percent of the passengers had symptoms of motion sickness. When placebos



Medication given ½ hour before sailing and then with each meal for 2 days. Each medication was given to 400 individuals.

Figure 2.—Effectiveness of prophylactic therapy.

were given, 27 percent had objective signs of seasickness. With M. S. P. only 17.8 percent became seasick. When benadryl was given as a prophylactic 9.7 percent had motion sickness. Dramamine protected all but 8.1 percent from motion sickness.

COMMENT

The difference in prophylactic value of 5.1 percent between placebo and no medication at all is not striking. However, the fact that 14 percent of those given a placebo after motion sickness developed recovered in 30 minutes and 60 were symptom-free at the end of 24 hours, whereas only 11 percent of those not receiving medication were symptom-free in 24 hours emphasizes the psychological aspect of motion sickness. This contention is supported by the three women who became nauseated while ascending the gangplank. These figures do not, however, support those who believe motion sickness to be merely a "state of mind"; the author is convinced that the psychological aspect plays a relatively minor role in motion sickness. Our results with M. S. P. were disappointing when compared with those reported by other observers working with this medication. In its favor is the absence of toxic symptoms observed by other investigators when the same dosage was used. The 29 percent of persons who had

not improved after 2 days of M. S. P. were given either benadryl or dramamine with complete relief of symptoms in a few hours in the majority of cases.

Benadryl proved more effective than dramamine in the period from 45 to 90 minutes after administration but was surpassed at that point and remained 3 percent less effective throughout the remaining time. Since benadryl has a hypnotic effect on many persons, it was at first thought much of its value was due to the extreme drowsiness produced. However, the administration of 2.5 mg. of benzedrine sulfate with each 50 mg. of benadryl eliminated much of the drowsiness and did not seem to change the therapeutic efficacy of the drug.

In our study of the drug, although dramamine did not prove as effective as reported by Gay and Carliner, it was dramatic in its allevation of motion sickness. The high cost of dramamine and the relatively little difference in therapeutic value as compared to benadryl does not merit its exclusive use.

Rectal administration of dramamine was deemed necessary in only one case, a woman 5½ months pregnant who could not retain anything taken orally. A retention enema of plain water with 100 mg. dramamine gave relief in 70 minutes and the patient was continued on oral therapy. In most cases, immediate repetition of the medication after vomiting was sufficient to control the motion sickness.

In addition to the treatment of the usual cases of motion sickness, seven women, all of whom were less than 5 months pregnant reported to sick bay with a history of vomiting several times daily before coming aboard ship and the condition had persisted. Two of the women had been receiving injections of pyridoxine without complete relief, the others had not consulted a physician. Both dramamine and benadryl proved effective in five of the seven cases. Either dramamine or benadryl was given until the vomiting ceased, the drug withdrawn and placebos given until the vomiting recurred, and then the other drug given in turn. One of the women responded only to dramamine and one did not respond to benadryl, dramamine, or pyridoxine; she was transferred to a naval medical facility at the first port. It was noted that none of the women benefited by the placebo which was substituted for the drugs without their knowledge.

TOXICITY

No toxic reactions were seen from M. S. P. although the literature states that hallucinations, mental cloudiness, change of heart rate, dry mouth, and cessation of sweating are all commonly found with overdosage.

No severe toxic symptoms resulted from benadryl; however, drowsiness was noted in 58.2 percent of a selected number of persons receiving

the drug who were asked to report if they noticed any unusual effects while taking the medication. One woman complained of a severe headache which ceased when the drug was withdrawn and returned when the benadryl was again given. The headache was so severe that she preferred to be seasick rather than continue taking the benadryl which had terminated the motion sickness. This patient had the only toxic reaction, other than drowsiness, seen in over 2,000 persons who have received benadryl aboard this vessel. In very few persons was the drowsiness caused by the benadryl intense enough to interfere with shipboard duties or activities. However, with the simultaneous administration of 2.5 mg. benzedrine sulfate and 50 mg. benadryl the drowsiness was eliminated or considerably diminished, and the therapeutic efficacy unchanged.

Cusic (*10*) reports that, because of the 8-chlorotheophyllin group, dramamine is the one antihistaminic drug which does not have undesirable side reactions. Gay and Carliner did not report any toxic reactions in their original work. The literature states, however, that side reactions should be expected occasionally.

The most common complaint against dramamine by our patients was the frequent and severe drowsiness. This finding was found in 36 percent of the persons receiving the drug and seemed to be just as severe as that seen with benadryl although it was 22 percent less frequent. The use of benzedrine sulfate, 2.5 mg. with each 100 mg. of dramamine, again eliminated the toxicity without diminishing its therapeutic value.

SUMMARY

1. Army Motion Sickness Preventive was considered the most effective drug until dramamine was reported by Gay and Carliner.

2. Dramamine proved effective in relieving motion sickness in about 91 percent in this series of cases but produced toxicity (drowsiness) in 22 percent of those persons receiving the drug.

3. Benadryl proved to be 88 percent effective in relieving motion sickness.

4. Benzedrine sulfate, 2.5 mg., given with each 50 mg. of benadryl or 100 mg. of dramamine eliminated much of the drowsiness.

EDITOR'S NOTE.—Benadryl and dramamine are similar in structure. Benadryl: β-dimethylaminoethyl benzohydryl ether hydrochloride. Dramamine: β-dimethylaminoethyl benzohydryl ether 8-chlorotheophyllinate.

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New Armed Services Catalog of Medical Matériel

Distribution of the new Armed Services Catalog of Medical Matériel has been completed. The new volume became effective 1 January 1950 and superseded the Army-Navy Catalog of Medical Matériel, and all changes thereto with the exception of the Standard Price Supplement, dated July 1949, which became an integral part of the Armed Services Catalog of Medical Matériel. The title "Army-Navy Catalog of Medical Matériel, Spare Parts Section," has been changed to "Armed Services Catalog of Medical Matériel, Spare Parts Section." The new catalog is designed to facilitate the incorporation of changes and additions as they are made. There are 8,142 items listed in the catalog, divided into 14 classes of which 5,476 are used jointly by the Army, Navy, and Air Force; 1,847 are used only by the Army and Air Force; and 819 are used only by the Navy. The items were selected and approved by the Armed Services Medical Matériel and Specifications Committee, after a comprehensive review. The catalog's index and cross-index simplify the location of an article in the catalog by its name and number. A conversion table has been provided, showing the new numbers given to items listed in the old Army-Navy Catalog of Medical Matériel. The joint Army-Navy procurement of medical supplies has been in effect since 15 December 1945 and since 1 July 1949, when the Air Force became autonomous, procurement of medical supplies has been accomplished on a joint Army-Navy-Air Force basis.

Progeria in the Adult (Werner's Syndrome)

Report of a Case

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Clifford P. Powell, *Captain (MC) U. S. N.*[1]

PATIENTS who look 20 to 30 years older than their stated age bring several conditions to mind, such as arteriosclerosis, Simmonds' disease, carcinoma, emphysema, and malnutrition. A group of syndromes associated with premature aging are those of Werner (progeria of the adult), Rothmund, and Hutchinson-Gilford.

Thannhauser (*1*) reviewed these entities completely and stated that more cases will be found if the condition is kept in mind. Other problems of interest arise: What comprises "growing old," the nature of arteriosclerosis, and the effects of the dynamic equilibrium of the endocrine systems?

Werner's syndrome was first described in 1904 by Otto Werner and named in 1934 by Oppenheimer and Kugel (*2*) who first reported the condition in the American literature. It has some or all of the following characteristics: (*a*) shortness of stature; (*b*) canities (premature graying of hair); (*c*) premature baldness; (*d*) scleropoikiloderma; (*e*) trophic ulcers of the legs; (*f*) juvenile cataracts; (*g*) hypogonadism; (*h*) tendency to diabetes; (*i*) calcification of blood vessels; (*j*) osteoporosis; (*k*) metastatic calcifications; and (*l*) tendency to occur in siblings. These were evident in members of family "K" as related by Werner (*3*). A typical case has early graying, premature baldness, tight atrophic skin over ankles, hyperkeratosis of the feet, leg ulcers, cataracts before the age of 30, a high-pitched voice, short stature, and some endocrine disorder as manifested by an enlarged thyroid. In general, signs of arteriosclerosis and premature aging are present. The condition is considered to be a recessive heredofamilial disorder with skin manifestations of "heredofamilial atrophic dermatosis with skin ulcers." Formes frustes may occur.

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Figure 1.—Complete alopecia.

CASE REPORT

F. B., a 45-year-old white man, a statistician by profession, was admitted to the United States Naval Hospital, Philadelphia, Pa., in March 1948, complaining of pain and ulcerations of both lower extremities, associated with intermittent attacks of pain in various joints.

Past history.—He was apparently well until 4 years ago while serving in the United States Army, at which time he was admitted to a hospital in Corsica for arthritis and arteriosclerosis. He had had intermittent pain in his legs and joints with leg ulcers that had failed to heal completely during the year prior to admission.

Between 1941 and 1947, he gradually became totally bald and in 1945 all the pubic and axillary hair disappeared (fig. 1). During this time many characteristics of aging were noted (figs. 2 and 3). He complained of generalized weakness and noticed a considerable loss of energy and sense of well-being during the past year.

Family history.—His mother and father died at ages 67 and 78, respectively. He has four brothers living and well, and a daughter by a previous marriage who is also well. No member of the family in any generation has had a similar condition so far as is known.

Physical examination.—The patient is a thin, short, white man appearing about 70 years of age. His skin shows generalized atrophy and wrinkling, most noticeable over the legs and hands with some lichenification around the ankles. Small fine white scales are present on most of the skin. He has complete alopecia. Numerous wrinkles are present about the eyes, associated with folds of loose atrophic skin hanging from the submental area. The lower extremities are a violaceous color; numerous healed and partially healed small ulcers are present on the

Figure 2.

Figure 3.

Figure 4.—Appearance of lower extremities.

Figure 5.—Clubbing of the toes.

anterior surface of both ankles (fig. 4). The dorsalis pedis and posterior tibial arteries have little pulsation. Clubbing of the fingers and toes is present (fig. 5). The brachial arteries are palpable and are hard and inelastic.

Laboratory examination.—The blood, urine, and electrocardiogram were normal; blood Kahn test negative; fasting blood sugar, 96.4 mg. per 100 cc.; alkaline phosphatase, 2.63 Bodansky units; blood uric acid, 2.8 mg. per 100 cc.; blood cholesterol, 337.5 mg. per 100 cc.; normal glucose tolerance curve; and the basal metabolism rate was plus 26 on repeated occasions. The urine 17 ketosteroids were 5.6; a low normal. Roentgenogram showed pulmonary emphysema with bullae in the upper lobes, and generalized periosteal thickening and increasing condensation throughout the long bones; the findings are consistent with pulmonary osteoarthropathy. Funduscopic examination showed no pathologic changes. Oscillometric readings are given in table 1.

TABLE 1

	Right leg	Left leg	Normal
Midthigh	2.5	1.0	8 to 15
Below knee	1.5	.75	5 to 12
Midleg	2.0	1.0	4 to 8

The laboratory examinations indicate emphysema, extreme impairment of the circulation in the lower extremities, and conflicting evidence of some endocrine disturbance pointing toward the thyroid. In most cases of Werner's syndrome various manifestations of endocrine involvement have been present such as: hypogonadism, hyper- and hypo-thyroidism and a tendency toward diabetes. In none of the cases reported has any definite endocrine basis been established.

Despite various forms of treatment including physiotherapy and administration of alpha-tocopherol, 50 mg. 3 times daily for 4 weeks with no demonstrable results, the condition of the lower extremities gradually became worse.

DISCUSSION

Although this patient definitely has evidence of bullous emphysema, extreme involvement of the circulation of the lower extremities, and arteriosclerosis; the signs of premature aging are so prominent that it could very well fit into the category of forme fruste of Werner's syndrome.

DIFFERENTIAL DIAGNOSIS

Rothmund's (4) syndrome is similar to Werner's except that many features such as cataracts and telangiectasis appear early in life between the ages of 3 months and 6 years; whereas, in Werner's these appear generally after the age of 20. The telangiectatic lesions appearing on the face, buttocks, or extremities in Rothmund's syndrome are not seen in Werner's. Furthermore, the skin in Rothmund's is not taut and tightly stretched over the underlying structures, but is thin and pliable, with no ulcerations. The skin disorder in this condition is called "heredofamilial atrophic dermatosis with telangiectasis." Many of the characteristics of Werner's syndrome may also be present.

Progeria of children with nanism (Hutchinson-Gilford's (*5*) (*6*) (*7*) (*8*) syndrome) appears within the first 3 years of life. They are dwarfs with a short life span (the oldest on record was 26 years of age at time of death). These patients are similar to those with Werner's syndrome in that (*a*) they are short and dwarfed; (*b*) they have short deformed extremities and a large abdomen; (*c*) their fingers and toes are short; (*d*) the skin is atrophic and taut; (*e*) there is a lack of hair; (*f*) they have sexual retardation; and (*g*) they also have diffuse arteriosclerosis, osteoporosis, and premature senile changes. They differ in that there is no familial tendency, no pressure ulcers, and no cataracts. Autopsy shows diffuse arteriosclerosis with no definite changes in the endocrine organs. Autopsy (*9*) in cases of Werner's syndrome generally shows about the same thing except that arteriosclerosis is generally not as pronounced.

Cataracts dermatogenes (neurodermatitis) "type Andogsky."—This condition is indicated by the presence of juvenile cataracts, ichthyosis, and neurodermatitis.

Myotonic dystrophy.—Some present all the signs of Werner's syndrome in addition to the muscular dystrophy and myotonic features.

Hereditary ectodermal dysplasia (10), dystrophy of hair and nails. "Type Widderburn" affects men only. The inability to sweat, hypotrichosis, and anodontia. "Type McKay and Davidson" affects both sexes. They can sweat, but their hair and nails are dystrophic. These two types result from defects in the ectodermal germinal layer; whereas in the Werner, Rothmund, and Hutchinson-Gilford syn-

dromes it is the consensus that they result from multiple germinal defects because they present recessive characteristics, are of heredofamilial occurrence, and because endocrine manifestation is only one of the multiple features.

SUMMARY

A case of possible atypical progeria in a man 45 years of age appearing to be 70 is reported for the purpose of stimulating attention to the syndrome of premature aging. It is believed other cases will be reported if the condition is kept in mind.

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Urinary Excretion of 17 Ketosteroids in Tetraplegic and Paraplegic Patients

A Preliminary Metabolic Report

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HAROLD A. LYONS, *Commander (MC) U. S. N.*[1]

EVER since Selye (*1*) introduced his theory of the adaptation syndrome, he and others have attempted to explain various conditions by this hypothesis. The chronic paraplegic patient with persistent bedsores, genito-urinary tract infections and renal calculi, gastrointestinal ulcers, and other lesions represents a situation when an organism is subjected to repeated stimuli over a prolonged period of time. The occurrence of systemic deterioration in these patients concomitantly with the appearance of such stimuli provoked the suggestion (*2*) that a humoral mechanism might be involved. Our interest in this problem was also stimulated by the fact that post-mortem examination of several of these patients showed considerable deposition of a substance resembling amyloid in the adrenal glands (*3*), and in each instance the cortex of the glands was most severely affected.

We became interested in the urinary excretion of the 17 ketosteroids in this type of patient as a direct result of these observations. In addition, it was believed that this would be an opportunity to evaluate the physiologic effect of interruption of the spinal cord on the excretion of these same products. Such observations seemed particularly pertinent since Bustamante (*4*) postulated a direct neural connection between the hypothalmus and the gonads, even though Reitman (*5*) recently discounted any such mechanism when he discussed the changes in the 17 ketosteroid excretion following frontal lobotomy.

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MATERIAL AND METHODS

The determinations of the 24-hour urinary excretion of the 17 ketosteroids (total neutral fraction) were performed by the Sloan-Kettering Institute, Section on Clinical Endocrinology, Memorial Hospital, New York, according to the method outlined by Engstrom (*6*). The results of this study in 21 patients, all men, are listed in table 1. The age of each patient is also included because of the difference in excretion of these substances in various age groups (*7*).

TABLE 1.—*Urinary excretion of 17 ketosteroids in tetraplegic and paraplegic patients*

Case No.	Age	Spinal cord level	Ketosteroid excretion (mg. 24 hr.)		Case No.	Age	Spinal cord level	Ketosteroid excretion (mg. 24 hr.)	
			Date	*Amount*				*Date*	*Amount*
1	24	C7	10–29	3.2	10	36	T5	12–17	13.8
			11–29	8.8	11	29	T10	11– 5	10.5
			12– 7	18.6				12–17	8.6
2	22	C6	10–29	12.6	12	20	T10	10–29	9.8
			11–12	15.0				12–17	20.8
3	27	T9	11–11	6.4	13	60	T11	11–24	5.7
			11–30	14.0	14	28	T4	10–29	4.0
4	21	C6	10–29	1.50				11–29	14.0
			11–29	23.6				12–17	8.4
			12–17	19.0	15	23	T9	11– 5	21.4
5	34	T12	11–12	17.8				11–30	16.0
			11–30	17.4	16	22	T12	10–29	1.1
6	24	T12	10–29	9.6				11–29	7.6
			11–30	13.0	17	23	L1	11– 5	10.10
7	21	T7	11– 5	21.4	18			11–24	24.0
			11–29	18.0				11–30	8.6
8	25	D10	10–29	8.0	19	23	T12	11–11	11.20
9	23	T12	10–29	7.7	20	24	C6	11– 5	10.9
			12–17	8.6	21	28	T5	11–11	9.9

NOTE.—The normal range of excretion in the urine of the 17 ketosteroids (TNF) for the age group 20 to 40 years is 8.1–22.6. (7).

RESULTS

The total number of determinations have been recorded, but it should be noted that some results (29 October 1948) tend to be very low. Since these were the first collections and determinations that were done and, particularly, since they were at great variance with other results in the same patient, we believe that no significance can be attached to them. They are reported for completeness only. The remaining values, however, are not indicative of an abnormal excretion of these substances, even though several reports seem to be lower than normal. This assumption is entirely warranted when it is remembered that there is a daily variation in these figures in the individual and that unless a result is repeatedly constant no real value can be attached to it (*8*).

Since both the testicles and the adrenal cortex are concerned with the appearance of these excretory products in the urine, case No. 13 was of special interest. In this instance the patient had had a bilateral orchidectomy for carcinoma of the prostate with metastases

to the spine. This result must also be considered normal in the light of Kimeldorf's work on rabbits (*9*). He found that there was a 41 percent decrease in the excretion of the 17 ketosteroids (TNF) in the urine following castration.

DISCUSSION

It is apparent that prolonged interruption of spinal cord function in man has no significant effect on the excretion of 17 ketosteroids (TNF) in the urine. It is surprising, however, that significant decreases were not noted in some instances; namely, in those patients who have had repeated infections and painful episodes as well as those with extreme liver disease (*7*).

Although further studies on the adrenal cortical function of these patients are in progress and still incomplete, these studies seem to indicate that hypofunction of the adrenal cortex is not associated with the so-called "paraplegic" state.

SUMMARY

The chronic paraplegic excretes a normal amount of 17 ketosteroids in his urine over a 24-hour period. The results reported here tend to exclude adrenal cortical insufficiency as the cause of the failure of some of these patients to react adequately to distressing stimuli.

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Circumcision of the Newborn

An Exact Technique for the Use of the Gomco Clamp

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FROM 15 March 1948 to 15 March 1949, 387 circumcisions on newborn infants were performed by the author and his associates with the Gomco clamp. During the first half of this period, 2 circumcisions had to be repeated because of postoperative phimosis caused by the removal of too little tissue at the initial operation. Since then an exact technique for the use of the Gomco clamp has been followed and there have been no postoperative complications. Although Pugh (*10*) condemns any type of preputial clamp because of the danger of secondary bleeding, there were no cases of postoperative hemorrhage in the entire series performed with the Gomco clamp.

Wolbarst (*12*), after an extensive study, concluded that at least 225 deaths from penile cancer and approximately twice as many nonfatal cases could be prevented annually in the United States by circumcision of all male children in infancy. Phimosis was universally recognized as the most important factor in penile cancer. We advise circumcision of all infants whose foreskin cannot be dilated sufficiently to permit easy retraction over the glans penis. The operation is performed on the fourth day of life but deferred if the infant weighs less than 5 pounds 8 ounces, or is clinically jaundiced.

A review of the literature reveals a variety of circumcision clamps in use. In 1907 Borey (*4*) described a clamp with much the same principle as the Gomco clamp but, from his description, less sturdy and more complicated. Since then many authors (*1*) (*2*) (*3*) (*7*) (*8*) (*9*) have described circumcision clamps, guides, and forceps of varied simplicity and ingenuity.

In 1935, Yellen (*13*) described a clamp developed by Aaron Goldstein, of Buffalo, N. Y. and used successfully in over 500 newborn circumcisions. In 1939, Brodie (*5*) reported 300 cases of infant circumcision with the Yellen clamp. According to a personal communication from the manufacturers, the present Gomco clamp is the same

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clamp with a few modifications that was described by Yellen. This is the clamp that was used in our 387 circumcisions.

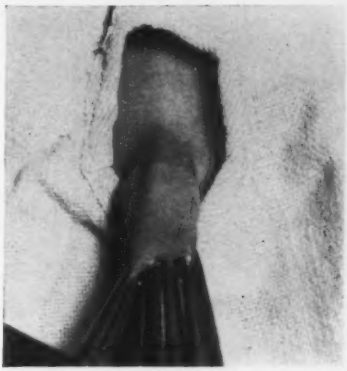

Figure 1.—Use of mosquito forceps.

TECHNIQUE

A mosquito forceps is attached to each side of the tip of the foreskin. The point of a third mosquito forceps is then introduced between the foreskin and the glans as shown in figure 1. By opening this forceps and rotating it on its longitudinal axis the adherent mucosa is partially separated from the glans penis.

A dorsal slit is then made with its apex 0.75 cm. distal to the corona, the outline of which may be seen through the foreskin when it is stretched slightly by traction on the mosquito forceps attached to the lateral margins of the foreskin (fig. 2). Dorsal veins in the foreskin may be readily seen and avoided when making the dorsal slit, thus the blood loss is negligible.

The mosquito forceps are then removed from the lateral margins of the prepuce and the prepuce is retracted back from the glans penis to completely free all the adhesions between the mucosa and the glans. All the smegma is carefully removed by wiping the coronal sulcus with a gauze sponge.

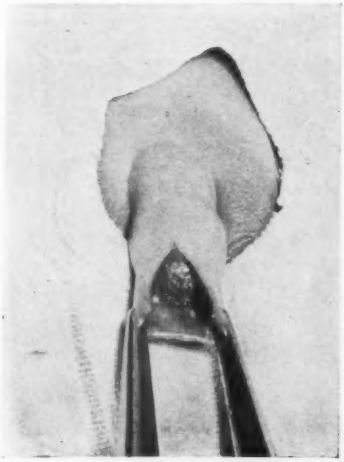

Figure 2.—Dorsal slit.

The cone of the Gomco clamp is then placed over the glans penis and the foreskin is pulled out over the cone. It is important to make certain that mucosa as well as the foreskin is over the cone. Two sizes of cones, a small (diameter 1.0 cm.), and a large (diameter 1.2 cm.), have been found to suffice for all newborn circumcisions.

The hole in the plate of the Gomco clamp is then easily slipped over the foreskin-covered cone and

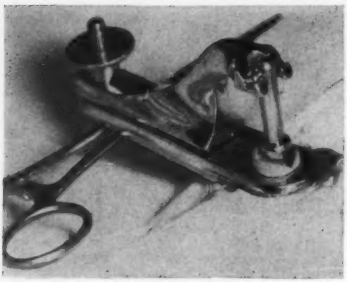

Figure 3.—Gomco clamp in place.

the foreskin pulled up evenly around the cone with plain thumb forceps. Reaching through the hole in the plate with mosquito forceps, attaching sutures to the foreskin to pull it through the hole in the plate, or other complicated procedures are not necessary. When the plate and the cone are assembled properly and screwed firmly into place, the apex of the dorsal slit should be 0.25 cm. distal to the margin of the hole in the plate as shown in figure 3.

After a 5-minute wait for pressure hemostasis, the foreskin is cut off flush with the margin of the hole in the plate. The clamp is then unscrewed, disassembled, and removed. As recommended by Walker (*11*) enough foreskin is left to cover the corona during relaxation of the penis (fig. 4). Figure 5 shows the foreskin retracted into the position in which it is left during the healing which prevents reforming of adhesions between the mucosa and glans.

The dressing used is similar to that described by Clarke (*6*) for adult circumcisions. The penis is wrapped in vaseline gauze and covered by a 4-inch square gauze pad, one layer of which contains a hole through which the penis is placed using the intact layer of gauze as a cover. The open ends of this dressing are tucked up under the infant's bellyband to complete the dressing.

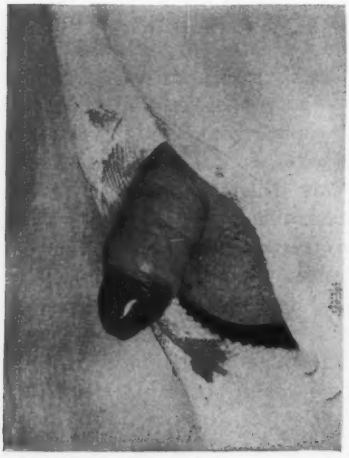

Figure 4.

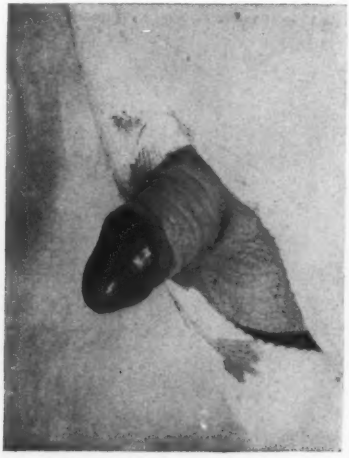

Figure 5.

CONCLUSIONS

1. Circumcision of the newborn is indicated in all cases in which the foreskin cannot be readily dilated and retracted over the glans penis.

2. Circumcision should be performed on the fourth day of life. The operation should be deferred in jaundiced infants and in infants weighing less than 5 pounds 8 ounces.

3. Routine performance of a dorsal slit results in negligible blood loss and permits an exact, measurable technique for the application of the Gomco clamp.

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Problems in Hearing

ARAM GLORIG, *M. D.*[1]

THE problem of testing hearing has been of great concern to the Army for many years but little progress was made until World War II. In the latter part of 1943 the deafened soldier became a definite source of difficulty. Many men had entered the Army with hearing below the minimal requirement because of poor testing at induction centers, and the acoustic trauma, blast, and barotrauma incident to modern warfare added more cases of deafness. To meet this problem, centers for rehabilitating deafened soldiers were developed.

Before any type of rehabilitation is attempted the amount of disability must be determined. Testing the hearing by whispered and spoken voice, coin clicks, watch ticks, and tuning forks is of little value because the output at the sound source is not controlled and the environmental noise level is high and variable (*1*) (*2*) (*3*). Single tests by these means were erroneous and when repeated gave confusing results (*4*). It follows then that these tests are useless for determining line of duty, progression, aggravation, eligibility for retirement, or amount of disability. If any of these are to be determined properly, reliable and consistently repeatable tests must be used. This led to the methods of testing now in use.

The primary function of the ear is communication. The most important means of communication is speech, therefore, a test which uses speech as a stimulus is essential. Any test of auditory acuity, however, based on the distance at which the low conversational or whispered voice can be heard cannot give a true measure of hearing because sound intensity varies inversely as the square of the distance. This means that the changes in intensity, as one varies the distance between subject and tester, vary only slightly at distances greater than 8 feet, and greatly at distances less than 8 feet (*4*). This is true provided the output at the sound source is constant. This brings us to the second source of error. No tester, no matter how well seasoned or trained, can maintain a constant spoken-voice level without electri-

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cal control. The variation may be as much as 100 percent even when a well-trained tester works under standard conditions. Another source of error is the variation in environmental noise in the place where the test is conducted. A test without earphones to be reliable must be performed without the interference of ambient noise because any ambient noise serves to cause error by distraction and masking.

Two tests are available—pure tone and speech reception audiometry. A pure tone audiogram is probably the most useful single hearing test we have at present. It requires a standard discrete frequency audiometer. The three sources of variation in pure tone audiometry are the instrument, the operator, and the patient.

To avoid variations of practical significance, a rough calibration of the instrument should be accomplished each morning or every other morning, and always on Monday morning. This calibration can be performed by checking the threshold of an operator or any other normal person with known auditory acuity. The greatest need for caution in handling the instrument relates to the receiver. Any severe jar is likely to cause a change in the receiver output. Each receiver is calibrated to match each instrument. Any change in the receiver will disturb the entire system.

In regard to the operator, pure tone audiometry demands meticulous attention to the details of technique. Unless close attention is paid to the patient, and thresholds are rechecked at each frequency, wide discrepancies will occur. In seeking the threshold it is best to approach it from above and below, alternately, four or five times. If the audiometer indicates a severe hearing loss and the patient seems to have only slight difficulty hearing conversation the source of the discrepancy must be sought. The patient must be placed in a position that makes it impossible for him to observe the operation of the audiometer. Changes should always be made in the dial settings when the interrupter switch is *off*. These and many other details are of the utmost importance.

The remaining variable is the patient. The pure tone audiometer is by no means an infallible barrier to malingering or psychogenic overlay. This can be summed up by saying that if malingering is intended its discovery will depend on who is the more clever—the tester or the tested. The operator should study the response of the patient. Is it sure? Is it repeatable at about the same level, at the same frequency after other frequencies have been tested? These are but two of the points to be noted about the patient's attitude during testing.

When completed, audiograms usually fall into the following classes: (*a*) normal (0 to 15 db[2]); (*b*) flat (any line greater than 15 db but

[2] Decibels.

nearly equal at all frequencies—fairly common); (*c*) falling curve (usually starting at 0 to 15 db for the frequencies 250 (256), 500 (512), and 1,000 (1,024) c/s [3] then dropping gradually or suddenly to levels greater than 20 db—very common); and (*d*) rising curve (the lower frequencies show the greater loss gradually rising to normal or slightly below normal—this type is relatively rare). Probably the most common exception to these classes is the pure tone audiogram with a normal curve, except for a dip at 4,000 (4,096) c/s varying from 20 to 60 db. This dip is of little or no significance. Another exception that is relatively rare is a **U**-shaped curve. It has normal values at each end of the sound spectrum, with values symmetrically falling in the middle and again symmetrically rising to normal.

The frequencies we are most concerned with in relation to speech are 500, 1,000, and 2,000 c/s. This is the speech range which extends from about 350 to 3,000 c/s. In general, if an average of these three frequencies is taken, the resulting figure will give a close approximation of the loss for speech in decibels. Hearing losses should be recorded as decibels of loss rather than in percentage. It is a mistake to attempt to interpolate between the 5 db steps on the audiometer since the resulting figure is merely a guess and it is not necessary to record steps of less than 5 db. If there is a question of the threshold not being as little as 30 and perhaps not as much as 35 db then 35 should be recorded.

Deafness may be classified as conductive, perceptive, and mixed. Conductive deafness is caused by a barrier to the conduction of airborne sound from the external ear through the middle ear to the cochlea. Any sound getting through to the cochlea is picked up, analyzed correctly, and carried to the central nuclei normally. Examples of this are otosclerosis, middle ear deafness, and foreign bodies in the external canal. Perceptive deafness is caused by malfunction of the receptive mechanism of the inner ear or any dysfunction of the auditory nerve trunk, cortical nuclei, and auditory area. Sound arrives at the cochlea normally, but at this point perception is faulty for both intensity and discrimination. Examples are deafness caused by acoustic trauma; toxic conditions such as quinine, nicotine, and streptomycin poisoning; meningitis; acoustic nerve tumors; Ménière's syndrome; presbycusis; and trauma to the auditory cortex. Mixed deafness is a combination of the preceding types.

In general, patients with a hearing loss in the better ear of less than 25 db in the speech range will have little difficulty performing military duty. There are patients, however, whose hearing loss lies between 20 and 30 db, who will complain of difficulty in situations which re-

[3] Cycles per second.

quire acute hearing, such as conferences, lectures, theaters, parties, and noisy places, particularly groups in which several conversations are carried on simultaneously. The treatment of this type of patient is also dependent on the amount of loss in the most severely affected ear. If the hearing is nearly equal in both ears difficulty will be less than if the poorer ear is much worse than the better ear. The treatment will be determined by the type of hearing loss also. A patient with a predominantly conductive loss will have relatively little trouble as compared with a patient with a perceptive loss, particularly if the pure tone audiogram shows a steep loss following 500 to 1,000 c/s.

This can be explained as follows: A patient with a conductive loss needs only an increased intensity to pass the obstruction to the airborne sound, after which the cochlea functions normally. In contrast, in perceptive deafness the cochlea is faulty, and although increased sound is perceived this sound is not analyzed correctly and the result is summed up by the statement, "I can hear you but I cannot understand what you are saying." Analyzing further, the vowels carry the strength of the words but discrimination is controlled by the consonants. The vowels are made up of frequencies below 1,500 c/s and the consonants above 1,500 c/s. This explains why some patients have more difficulty than others and why some words and voices are more easily understood than others.

Speech reception audiometry seeks a person's auditory threshold and discriminatory power for speech by the use of special word lists presented through a controlled amplification system. This may be conducted by a monitored live voice over earphones or in a sound-controlled situation without earphones. It has no relation to the low conversational voice or whispered voice tests.

After a diagnosis and evaluation have been made, and all definitive treatment has been accomplished with no improvement, rehabilitation is mandatory. Rehabilitation of the deafened soldier is a specialized job and should be attempted only by trained personnel. At present the Army has the world's finest center for rehabilitating deafened persons. Its purpose is to study, evaluate, and rehabilitate deafened soldiers in such a way as to make them useful to the Army. Any soldier who complains of difficulty with his hearing should be studied carefully and not pushed aside as a malingerer or chronic complainer. If an audiogram shows him to have a loss of 25 db or more in the speech range he should be sent to the Audiology and Speech Correction Center at Walter Reed General Hospital for study. Conversely, if his hearing loss is less than 25 db, or he has one ear with less than 25 db loss, there is no need for rehabilitation. Severe deafness in one ear, with better than 25 db in the good ear, will cause little or no disability; in the past 2½ years many patients have been sent to this

center needlessly because of ignorance of this fact. On the other hand, there are many who have not been sent here because of improper study or no study at all.

This center has returned to duty patients of ranks from privates to lieutenant generals with benefit to the patient and to the military service. Patients often enter this clinic tired, bewildered, and psychologically beaten but leave after a few weeks with a new understanding of their problems and a completely renewed confidence in their ability to perform their military duties. It is now the policy of the Army to send back to duty any patient whose hearing is improved to 20 db or better by a hearing aid although these men cannot perform combat duty. The instrument would break down under combat conditions, but there is no reason why such men cannot do all other types of duty. It behooves the officers responsible for assigning these men to assign them to noncombat duty. Today's armies are highly specialized, and many men who have been deafened in the Army have experience that can be useful if they are properly assigned. On the other hand, these same soldiers without rehabilitation are less useful, and because of fear of disfavor from a misunderstanding superior officer may neglect to report their progressing disability.

The deafened person develops a peculiar psychology. He becomes an introvert and seeks to hide his disability. Many men who are deafened have been considered disciplinary problems because of failure to hear commands or instructions. Rehabilitation involves more than issuing a hearing aid that is nothing more than an amplifying system reduced to a convenient size. Because deafness is largely influenced by the patient's psychologic make-up and response to amplified sound, just any device will not answer the purpose. A fitting procedure is necessary to determine which, if any, of the numerous makes will give the best results as determined by controlled tests. After this the patient is given a training course in the use and care of the aid. This course is designed to show the patient how to get the most out of his instrument and to convince him that by its proper use he will overcome most of the difficulties he first encountered. Added to this are courses in lip reading, in increasing powers of observation, and in correcting speech defects. Each has its share of psychotherapy also.

This center is equipped to deal with any type of speech defect, including stuttering, aphasia, defects caused by articulatory dysfunction (whether traumatic or psychologic), defects resulting from deafness, and esophageal speech training after laryngectomy. The staff of this center has become expert in making decisions concerning the deafened soldier's ability to perform his military duties and with few exceptions any man returned to duty from this center can do mili-

tary duty if he so desires. Patients are routed to this center after being studied by the otolaryngologist of the referring hospital. If a patient is considered to have defective hearing within the limits previously outlined, application is made through the regulating medical officer, Office of the Surgeon General, for transfer to Walter Reed General Hospital. All problems regarding defective hearing must be decided by the Audiology Service, Walter Reed General Hospital (*5*).

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Scrub Typhus in Assam and Burma [1]

The incidence of scrub typhus on the basis of case rates and isolation of rickettsial strains from chiggers and tissues varies in 9 areas near Ledo, Assam. The percentage of chiggers that were *Trombicula deliensis* (*Walch*) in samples from these areas varied from 13 to 96 percent. *T. deliensis* was most prevalent at the 3 areas undoubtedly most dangerous with respect to scrub typhus, constituting 60, 74, and 96 percent respectively of all chiggers sampled, and was least abundant in areas reporting no cases and considered relatively less dangerous. Samples from the hyperinfective areas were most likely to consist entirely of *T. deliensis*. In one very dangerous area, 50 of 75 samples consisted entirely of this mite. In the less infective areas *T. deliensis*, reported in every batch of chiggers from which rickettsial strains were isolated, never appeared in more than 10 percent of the samples.

In the most dangerous area 12 mite strains were isolated in 30 attempts, and over 99.5 percent of the chiggers sampled were *T. deliensis*. In 46 instances, all the mites sampled were of this species. On the basis of abundance, its habits, and its chiggers, and because of the strains isolated from its chiggers and tissues, *Rattus flavipectus yunnanensis* is considered to be important in the epidemiology of scrub typhus in the Ledo area. Shrews are involved in the epidemiology of this disease. Data were presented indicating that *T. deliensis* was more abundant on various species of rats taken in grassy terrain and scrubby growths along the roadside in North Burma than on hillsides of the contiguous primary jungle. *T. deliensis* was much more prevalent in the wet season than in the dry season, although it was found throughout the year.

[1] TRAUB, R.: Observations on tsutsugamushi disease (scrub typhus) in Assam and Burma. Abstr. Am. J. Hyg. **50**: 361–370, Nov. 1949.

Pathologic Features of Yellow Fever in Panama

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CARL M. JOHNSON, *M. D.*[1]

THE continuing occurrence of deaths from yellow fever among the native farming population in the Republic of Panama will afford an unusual opportunity to study the pathologic features of this disease, and to observe the involution of the liver lesion and the progress of the lower nephron (hemoglobinuric) nephrosis, when death is delayed.

Although an intensive rural vaccination program has been completed by the Health Departments of the Republic of Panama and the Panama Canal, the migration of farmers from many remote localities of the interior to the yellow fever zone, particularly to the newer agricultural settlements along the Transisthmian Highway, makes it difficult to eradicate the disease. One recent victim is known to have refused vaccination. Since the initial outbreak in November–December 1948, there have been three additional proved deaths from yellow fever among unvaccinated farmers working in new clearings or engaged in felling trees. Two of these occurred in August and one in September 1949. During the rainy season, and particularly in November and December, with the last flurry of insect activity before the dry season, an increase in deaths is anticipated. Specimens from all organs at autopsy are now being referred to the Board of Health Laboratory, Gorgas Hospital, for diagnosis and complete histologic examination.

Ranking high among the relatively recent discoveries pertaining to yellow fever is the characteristic microscopic liver lesion, one of the most pathognomonic histologic patterns to be seen under the microscope. Stoke's discovery that the virus of yellow fever could readily be transmitted to the *Macacus rhesus* monkey initiated the chain of events leading to the discovery of the sylvan origin of the disease. The modification of the technique of the Pfeiffer phenomenon to the mouse-protection test provided a practical diagnostic test

[1] Board of Health Laboratory, Gorgas Hospital, Ancon, C. Z.

and the development of an effective vaccine provided a practical control measure.

Of importance was Hoffmann's (*1*) recommendation, in 1928, that the histologic specificity of the liver lesion of yellow fever be made the basis of routine diagnosis. The pathologic findings in yellow fever may have been well known to a few investigators, but they certainly were not common knowledge. A clear description did not appear until 1929 when Penna and Figueiredo (*2*) stressed the differential diagnostic significance of the lesion. Klotz and Belt (*3*) summarized the liver findings in 1930. Councilman (*4*) had earlier described

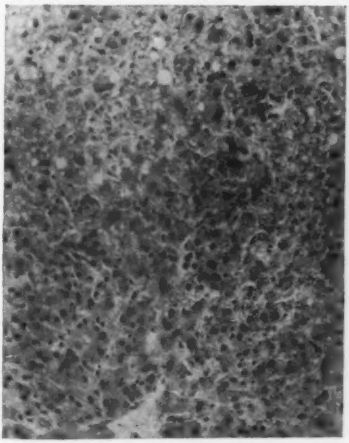

Figure 1.—Liver in delayed death. Councilman's material from necrotic polygonal cells being extruded into sinusoids.

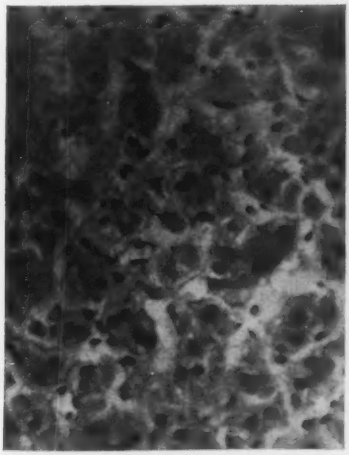

Figure 2.—High-power appearance of an area rich in Councilman bodies.

the characteristic liver necrosis that is now associated with his name, but he did not recognize the lesion as specific for yellow fever. In 1912, da Rocha Lima (*5*) described midzonal necrosis as characteristic of yellow fever, and this concept dominated the literature for many years without proper evaluation of the pathognomonic hyaline Councilman bodies. Implementation of Hoffmann's recommendation was effected in Brazil in 1930, and the diagnostic value of routine histologic examination of the liver was quickly established. The Viscerotome Service of Brazil, Bolivia, and Colombia contributed materially to the discovery of the sylvan form of the disease when Soper, Rickard, and Crawford (*6*) observed its reappearance in the absence of *Aedes aegypti* mosquitoes in the rural area of Espirito Santo, Brazil, in March 1932, and in the isolated village of San Ramon, Bo-

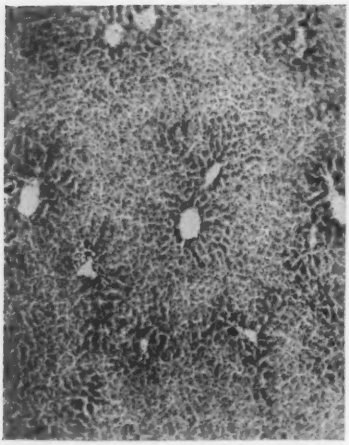

Figure 3.—Typical midzone necrosis in yellow fever.

Figure 4.—Peak of degeneration in Councilman bodies, with midzonal hemorrhage in liver lobules.

livia, in May 1933. The initial diagnosis of the recent Panamanian cases (*7*) was as easy as Hoffmann predicted in 1928, but was materially facilitated by familiarity with a slide prepared in 1941 from a Bolivian specimen and used since 1942 in a reference set on the pathology of tropical diseases. With such a guide the diagnosis was indisputable.

Histologically the gross pattern of the liver lobules is not materially disturbed although the cords are jumbled. Central veins and portal islands are readily distinguishable. There is no central necrosis that disturbs the outlines of the central veins. Necrosis involving the midzones of the lobules extends inward to two or three rings of cells bordering the central vein and to from one to four rows of cells which demarcate the perimeter of the lobules; these cells show minimal involvement. This necrosis is distinctive not only in its distribution, but also in its character. Councilman bodies, consisting of discrete hyalinelike eosinophilic masses of polygonal cell cytoplasm, are sprinkled in a salt-and-pepper fashion throughout the lobule, contrasting in color with the basophilic cytoplasm of the uninvolved cells and the remnants of partially involved cells (figs. 1, 2, 3, and 4). Some polygonal cells show only partial hyaline necrosis without detachment of the eosinophilic portions of their cytoplasm.

The degree of this necrosis varies in different lesions. In some, practically no normal polygonal cells remain and the entire lobule is diffusely involved, including the central and peripheral rings of cells.

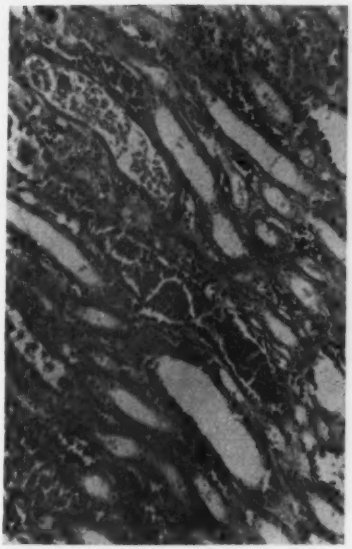

Figure 5.—Hemoglobin casts in collecting tubules of kidney in yellow fever.

Figure 6.—Higher magnification of hemoglobin casts.

In others the necrosis is light and scattered, attaining its maximum density in the midzones. Polygonal cells showing the change in the Councilman bodies are usually wholly involved at the peak of the process—their shrunken nuclei often resembling a crescent on the cell edge, or the nuclei are missing. These cells appear as distinct, irregular, pink hyaline spheres or ovoids, and are often fragmented, resembling red blood cells. In the most recent involvement the liver shows midzonal hemorrhage, the red blood cells being distinguishable from the Councilman's fragments by their orange color.

Fatty degeneration is diffuse in character, but its degree in some cases varies inversely with the degree of degeneration of Councilman bodies, while in others the two degenerative processes coexist. There is some tendency for the fatty degeneration to spare the central zones. Nuclear inclusion bodies have not yet been demonstrated, presumably because of partial neutralization of the virus by the development of a protective antibody before death. Portal periductal and perivascular lymphocytic infiltration is common and may be associated with polymorphonuclear cell infiltration. In a recent case, in which death was delayed until the tenth day of illness, the superimposed factor of a peripheral zone necrosis with extensive polymorphonuclear cell infiltration accompanying the typical liver

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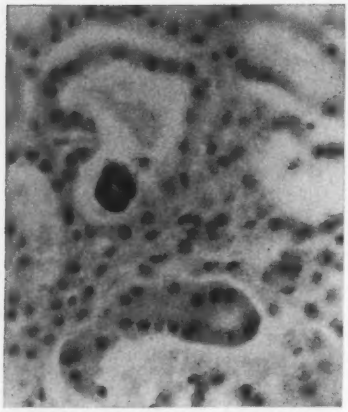

Figure 7.—Hoffmann body in a proximal convoluted tubule of kidney. This is a characteristic finding in yellow fever.

lesion was seen. In this case the kidneys also showed a fully developed lower nephron nephrosis, with the typical orange casts of hemoglobin (figs. 5, 6, and 7).

Although the liver lesion of yellow fever is described as specific and is not easily confused with other lesions, such as those of epidemic hepatitis, much still remains to be learned about it. It is curious that under certain circumstances in deaths from burns, a lesion said to be indistinguishable from it has been reported—an observation that may be of great importance in determining the pathologic changes in these entities (*8*). The mechanism whereby the liver is cleared of Councilman's material (if the patient survives to the tenth day or longer, when the chief obstacle to recovery is the lower nephron (hemoglobinuric) nephrosis) is also deserving of careful study. In one of the cases occurring in August 1949, movement of this necrotic material into the sinusoids was noted exactly as Councilman described it in 1890. The first case in the series reported by Elton and Herrera (*7*) did not present a typical histologic liver lesion, yet conformed epidemiologically, clinically, and pathologically with yellow fever. Future studies may throw light on the existence of possible anomalies in the histologic pattern of the entity or, perhaps, of other sylvan diseases simulating yellow fever in all respects except for the liver lesion.

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EXPLORATIONS INTO THE PHYSIOLOGIC BASIS FOR THE THERAPEUTIC USE OF RESTRICTIVE BANDAGES IN THERMAL TRAUMA. AN EXPERIMENTAL STUDY, by Frederick W. Rhinelander, M. D.; John L. Langohr, M.D.; and Oliver Cope, M.D. Archives of Surgery 59: 1056–1069, Nov. 1949.

Many authorities have advised pressure dressings and plaster casts for the local treatment of burns because these tend to limit swelling of the wound or, as in the case of plaster casts applied immediately after injury, prevent swelling without interfering with arterial blood flow, oxygenation, or nutritional environment of the tissues. Occlusive pressure dressings restore tissue pressure which is normally dependent upon an intact integument. Thus, pressure dressings aid venous return flow and limit both venous and lymph stasis. Pressure dressings are of value in preventing loss of plasma from the circulation, promote comfort, and so reduce the incidence of wound infection.

The experimental work of the authors emphasizes the clinical benefit derived from pressure dressings, but points out that although such treatment probably reduces the loss of plasma into the burn wound their findings were not conclusive. They noted that plasma from a burn wound is not sufficiently reduced by a plaster cast for the lymphatics to be able to carry and return it all to the blood stream. The lymph therefore piles up in the interstitial spaces proximal to the cast, and edema slowly reaches the volume it would have been had plaster cast dressing not been applied.

The clinical benefits which accrue from the use of restrictive dressings come from the immobilization of the wound. Motion of the burn wound increases the lymphatic flow and displaces edema proximally in the interstitial spaces; both have the effect of lowering tissue pressure in the wound and permit augmented seepage from the capillaries.

Restrictive immobilizing dressings are indicated in the care of burn wounds but they must not be used with the idea that the need of plasma to prevent shock will be reduced. The improper application of a plaster dressing carries with it the danger of gangrene.—*Abstract.*

About the Army Medical Department

PAUL I. ROBINSON, *Colonel, MC, U. S. A.*[1]

IN a previous article[2] a report of a visit to a number of stations in the United States was made. The questions that were asked by Medical Department personnel at that time were tabulated and answered in the light of current knowledge. Subsequent correspondence indicated that personnel in those places not visited also had many of the same questions in mind and appreciated the discussion. We have recently paid a similar visit to medical installations in Hawaii and the Far East. In Hawaii, the entire medical service for the Army is rendered by Tripler General Hospital. The Navy and Air Force have small dispensaries from which consultations and patients needing hospitalization are sent to Tripler General Hospital. Army, Navy, and Air Force officers comprise the staff at that hospital. The excellent working relationship between them leaves little to be desired. Congeniality and cooperation in professional as well as administrative relations were abundantly in evidence. A council composed of senior medical officers of the Army, Navy, and Air Force meets periodically to iron out minor difficulties and to formulate operating policies.

In Japan, the medical service is widely dispersed, corresponding to the distribution of troops. All hospitals, with one exception, are in permanent prewar buildings, many of which were originally constructed as hospitals. The medical service, without exception, was of the highest order. The relationship between Medical Department personnel and commanders whom they served was beyond reproach. Commanders everywhere had the highest praise for their medical service. Wives of officers and enlisted men in Japan were well satisfied if not enthusiastic about their living conditions. Much has been done in the way of stocking post exchanges with the necessities of life from the United States. A busy social life is carried on and a reasonable amount of household help is available. Many of the wives have

[1] The Personnel Division, Office of the Surgeon General.
[2] Bulletin of the U. S. Army Medical Department, May 1949, pp. 371–374.

taken great interest in Japanese culture and their conversation is most stimulating. Many have obtained, for reasonable prices, rugs, silverware, china, and cloisonné, damascene, and lacquer articles produced in Japan or China.

In Okinawa there is a scarcity of permanent buildings but construction is in progress. Nowhere is one confronted by a greater challenge to accomplishment. The spirit with which the personnel there are working to improve conditions is heartening. Attractive surroundings and efficient service must surely result from their endeavors. The wives there have entered into this spirit and are proving themselves a credit to their heritage.

In the Philippines, Army and Air Force medical personnel are jointly rendering medical service at Clark Air Force Base. Army units are rapidly finishing their work and leaving the Philippines. The Army continues to operate a hospital at Fort McKinley for the Philippine Scouts. All personnel continue to enjoy their service in the Philippines as they have in the past.

Our Navy operates the only hospital in Guam, and Army and Air Force medical personnel serve on the staff of this hospital. Army dispensaries are operated by Army medical personnel in an efficient manner and consultations are referred to the naval hospital. Morale is high and the joint operation is completely successful.

Medical personnel who so desired were interviewed at every station visited. Many had personal problems and no attempt will be made to enumerate them, although many others may have similar problems. Some of the questions of a general nature are discussed here.

Q. What will be the result of the closure of hospitals in the United States on the training program?

A. There are sufficient approved spaces in the remaining hospitals to accommodate all residents and interns. Coming in the middle of a training period—since only emergency cases could be admitted after 15 February 1950—the personal inconvenience of some officers in the program was unavoidable. The Army can fulfill its commitments to everyone in the program who is selected to advance and to everyone selected to enter the program in July 1950.

Q. What has been the reaction of the residents who are to be taken out of the training program and sent overseas for 3 months this summer?

A. Information from all of the hospitals indicates that quotas for each of them were filled with volunteers. Each officer will re-enter the program when he returns and, if he qualifies, will stay until he completes his training. The Department of the Army General Staff and the staffs of overseas commands have considered this solution to

the medical problem of this summer a commendable one. We expect all of these young officers to have a professionally profitable service as well as an interesting trip.

Q. Can officers who transferred to the Air Force transfer back to the Army if they desire?

A. Yes. Transfers of personnel between the Army and Air Force were extended by Public Law 216, Eightieth Congress, for 1 year. This means that until 26 July 1950 transfers are legally authorized. Agreement between the Army and Air Force on each transfer is required. More than 100 transfers have been made since passage of the law.

Q. Are transfers between the Army and Navy so authorized?

A. No. If one desires to come into the Army from the Navy, or vice versa, it is necessary that he resign his commission and apply for a commission in the other service. There is a tacit understanding between all the services that resignation from a Reserve commission to accept a Regular commission in any of the services will be approved. The applicant should specify his preference of service.

Q. What is the status of the legislation to allow nurses over 35 years of age to enter the Regular Army if they have had several years of active duty?

A. This bill has been passed by the House of Representatives and it is expected that it will pass the Senate before adjournment. If passed as currently written, it will authorize a qualified nurse to enter the Regular Army if she entered on active duty prior to 16 April 1947 under the age of 35 years and either served continuously on active duty to the current date or was separated subsequent to 12 May 1945.

Q. What is the status of the legislation to allow women doctors, dentists, veterinarians, and allied medical specialists to be commissioned in the Army Medical Department?

A. This bill also has passed the House of Representatives and it is hoped that it will pass the Senate before adjournment this year. Difficulties in coordination of this bill have resulted from the fact that the Navy, while it had no objection to the Army and Air Force having this authority, did not desire to participate in its provisions. Oddly enough, the Navy, under the legislation act pertaining to the WAVE, may commission women doctors in the Navy and permit them to have some of the privileges of other medical officers. The Army cannot do this under the legislation pertaining to the WAC.

Q. Why are not the tours of duty in overseas stations the same for nurses of all three of the Armed Forces?

A. This question might be broadened to include all personnel. The Army, Navy, and Air Force each determine the length of stay in overseas station for their own personnel. For women components,

however, special conferences have been conducted in the Office of the Secretary of Defense to determine if it is feasible and desirable to set uniform tours that may vary from those of male officers and enlisted men; and it has been recommended that women in each of the departments should serve the same tours as the male personnel of their respective service.

Q. Is it possible for a medical officer to extend his tour of duty for 1 year in Europe?

A. There is a policy that an officer must serve for 1 year in the United States before being returned to an overseas station. Because of the general shortage of doctors and dentists, however, it is likely that exceptions could be made in their cases. Anyone desiring to extend his tour should write to the Office of the Surgeon General in order that exceptions may be requested and instructions can be given him.

Q. Why do promotion criteria often discriminate against an officer? For example, an officer might be in the zone of consideration for promotion if he were a Reserve officer on active duty rather than a Regular Army officer.

A. It is fully realized that such cases do occur each time a zone of consideration is announced. The officers most affected are those, who though highly deserving, were denied promotion during the war simply because of limitations imposed by Tables of Organization or Distribution. To comply with existing regulations, it is required that Regular Army officers be arranged on a roster in order of their permanent seniority and non-Regular officers in order of their temporary rank. Based on the estimated vacancies, the zone of consideration for each of these two rosters is established. The number of Reserve and Regular Army officers included in the zone of consideration must be in direct proportion to the total number of officers of each group. By requiring Regular Army officers to have a specific number of years for promotion purposes, plus a specified date of rank, the most senior officers, from the standpoint of permanent grade, are considered for promotion prior to their juniors. To extend a zone of consideration to include Regular Army officers who would meet the Reserve criteria would disrupt the Regular Army promotion sequence, thereby creating a situation that probably would be even less desirable than the present system. In the long run, probably fewer officers will be discriminated against by the rigid application of the present limitations. In other cases Reserve officers appear to be discriminated against. All cases of apparent inequity arise from the promotion policies extant during the war when centralized control was not maintained.

Q. What are the possibilities of Reserve Medical Service Corps officers remaining on active duty in the future?

A. All Medical Service Corps officers must decide before the termination of their present categories whether or not they will apply to accept the grade of master sergeant. The Pharmacy, Supply and Administrative Section in the Regular Army Medical Service Corps is filled and only a few are commissioned each year through the medium of competitive tours. There will be a need, however, for as many Reserve officers on active duty as Regular Army officers in this section for many years to come. Each officer should look critically at his own case and make up his mind about his future. Some will have a good chance of serving for many years and at the same time receive training that will be to their advantage when they return to civil life. Others should consider accepting the grade of master sergeant. Still others may have an opportunity of completing a career on officer status.

Q. What will be the future assignments for physical therapists, dietitians, and occupational therapists in the United States now that so many hospitals are to be closed?

A. With the closing of the hospitals it will be necessary that transfer of all but the most difficult of medical cases to the general hospitals be curtailed. The training program is beginning to produce physicians, nurses, and women specialists in such quantities that more complete medical care can be given in certain station hospitals. There are few Army hospitals of less than 250 beds left. There is every indication that Army medical practice in the future will be one of the most ideal group practices existing anywhere in the medical profession, wherein all components of the Medical Department will be represented in almost every station hospital.

BOOK REVIEWS AND BOOKS RECEIVED

Publishers submitting books for review are requested to address them as follows:

The Editor,
UNITED STATES ARMED FORCES MEDICAL JOURNAL,
Bureau of Medicine and Surgery, Navy Department,
Washington 25, D. C.

(For review)

HELP YOURSELF TO BETTER SIGHT, by Margaret Darst Corbett. 218 pages. Prentice-Hall, Inc., New York, N. Y., publishers, 1949. Price $2.50.

This book, intended for lay persons, is a plug for the Bates method of treating refractive errors without glasses. Despite impressive testimonials this method is based on certain premises which, if not wholly unsound, are highly controversial. Chief among these is the idea that the eye may accommodate to near and distant vision through changes in the shape of the eyeball effected by the *extrinsic* ocular muscles. The advice to expose the eyes to direct sunlight ignores the evidence that such exposure predisposes to the formation of cataracts. Our orthodox ophthalmologists agree that the doctrine of relaxation, general and ocular, has much to commend it and that it may benefit selected patients, but the author in her enthusiasm gives no indication that there should be any selection of patients or that harm might result from the application of this method to some patients. In fact, claims are made that the methods employed have cured strabismus, astigmatism, presbyopia, subtotal blindness, and color-blindness with deafness thrown in for good measure. The pay-off occurs on page 186 where the highly esteemed Ishi Hari charts are referred to as a clever bit of subversive work designed primarily not to detect color-blindness but to keep healthy American men out of our Armed Forces! The book has no index.—*Lt. Col. W. G. Brandstadt, MC, U. S. A.*

AN INTRODUCTION TO ZEN BUDDHISM, by Daisetz Teitaro Suzuki, D. Litt., *Professor of Buddhist Philosophy in the Otani University, Kyoto.* Foreword by C. G. Jung, M. D., LL. D., D. Litt., D. Sc. 136 pages. The Philosophical Library, New York, N. Y., publishers, 1949. Price $3.75.

Dr. Suzuki is the greatest living authority on Buddhist philosophy in general and Zen Buddhism in particular. Republication of this book, written in 1934, is part of a project to republish all his works, new and old, because none have been available since the war. Dr. C. G. Jung, in a 20-page foreword, paves the way by attempting to disabuse the Western mind of misconceptions. Suzuki

attacks the problem by showing first what Zen is not. He then attempts to present the positive side of the picture, but Westerners find Zen so difficult to grasp that other and more comprehensive works must be digested before an adequate understanding is reached.—*Col. W. F. Bowers, MC, U. S. A.*

ALLERGY IN THEORY AND PRACTICE, by Robert A. Cooke, M. D., Sc. D., F. A. C. P., *Attending Physician and Director of the Department of Allergy, the Roosevelt Hospital, New York City,* in association with Horace S. Baldwin, Robert Chobot, R. Clark Grove, Joseph Harkavy, Selian Hebald, Michael Heidelberger, Paul Klemperer, Louis Schwartz, W. C. Spain, Dudley D. Stetson, Albert Vander Veer, Mathew Walzer, and Margaret B. Strauss. 572 pages, illustrated. W. B. Saunders Co., Philadelphia, Pa., publishers, 1947. Price $8.

This book, written by one of the foremost practicing allergists in this country in conjunction with many associates, is an excellent textbook. The early chapters rapidly review the fundamental facts and experiments in immunology which form the basis for the present concepts of allergic mechanisms and clinical diseases. An earnest attempt is made to point out the gaps in our knowledge and to stimulate interest in further research.

The importance of a careful, complete history in all allergic conditions is stressed, and there is an excellent section on skin testing, its techniques, interpretation of reactions, and limitations.

Each of the common allergic conditions is covered. The section on bronchial asthma is outstanding and that on allergic dermatitis very good. The presentation of the material in the chapters on allergic rhinitis could have been improved.

It is worth noting that this book very definitely emphasizes opinions of the authors and only occasionally is there mention of other points of view. However, for the young medical officer in the service without special training who is forced by circumstances to treat allergic patients, this volume can be recommended most highly.—*Lt. Col. W. H. Diessner, MC, U. S. A.*

THE STORY OF SCABIES, Volume I, The Prevalence (Civil and Military), Prevention and Treatment of Scabies, and the Biology of Acarus Scabiei, from the Earliest Times to the Beginning of World War II, by Reuben Friedman, M. D., *Associate Professor of Dermatology and Syphilology, Temple University School of Medicine; Fellow of the College of Physicians of Philadelphia; Member of the Philadelphia Dermatological Society, American Academy of Dermatology and Syphilology, Society for Investigative Dermatology, and American Association of the History of Medicine; Corresponding Member of the Italian Society of Dermatology and Syphilography and the Cuban Society of Dermatology and Syphilography; Diplomate of the American Board of Dermatology and Syphilology.* Foreword by Carroll S. Wright, M. D., *Professor of Dermatology and Syphilology, Temple University School of Medicine.* 468 pages, with 114 illustrations and 36 tables. Froben Press, Inc., New York, N. Y., publishers, 1947. Price $7.50.

Dr. Friedman, who is an international authority on the subject of scabies, has collected in volume I of a projected series of four volumes, material previously published in 1941 and 1942. Future volumes will be devoted to more recent advances in the study of Scabies Since World War II; The History of Scabies; and Classical Descriptions Relating to the Mite as Well as the Disease.

The reader never ceases to be amazed at the meticulous detail of Dr. Friedman's study of a disease and its causative acarina. There are extensive excerpts of descriptions of the mite, the disease, and the treatment from the earliest medical records available relating thereto, with astute conclusions as to their accurate or inaccurate relationship to the subject.

Volume I of the series will appeal primarily to the medical historian and the student of entomology. The dermatologist will learn much of the history of his specialty by reading this work as scabies has held the limelight in dermatology until recent times.

The style makes pleasant reading, the illustrations are excellent, but some of the tables are poorly produced.—*Lt. Col. V. R. Hirschmann, MC, U. S. A.*

THE PRACTICE OF REFRACTION, by Sir Stewart Duke-Elder, K. C. V. O., M. A., D. Sc. (St. And.), Ph. D. (Lond.), M. D., F. R. C. S., Hon. D. S. C. (North Western), *Surgeon-Oculist to H. M. The King; Knight of Grace of the Order of St. John; Consulting Ophthalmic Surgeon to the Army and the Royal Air Force; Director of Research, Institute of Ophthalmology, University of London; Consulting Ophthalmic Surgeon, Moorfields Westminster and Central Eye Hospital; Ophthalmic Surgeon, St. George's Hospital.* 5th edition. 317 pages; with 216 illustrations. The C. V. Mosby Co., St. Louis, Mo., publishers, 1949. Price $6.25.

In his typical straightforward style, the author presents the basic principles of physiologic optics and of their interpretation in the human eye. He then discusses the common errors of refraction; the anomalies of refraction; eye muscle imbalance; and the various clinical examinations of the patient that should be performed in a complete refraction.

The final chapter, on the making and fitting of lenses, is well done, especially the concise appraisal of the present day status of contact lenses.

One of the deficiencies of this volume is the lack of a bibliography, which is so necessary in a book that covers most subjects in a rather matter-of-fact manner, when in reality much difference of opinion exists concerning many of the topics under discussion.—*Capt. A. J. Delaney, (MC) U. S. N.*

KAYNE, PAGEL, AND O'SHAUGHNESSEY'S PULMONARY TUBERCULOSIS, Pathology, Diagnosis, Management and Prevention, revised and partly rewritten by Walter Pagel, M. D., *Pathologist, Central Middlesex County Hospital, London;* F. A. H. Simmonds, M. A., M. D., D. P. H., *Medical Director, Clare Hall County Hospital, Middlesex;* N. MacDonald, M. B., M. R. C. P., Ed., *Physician to the Chest Clinic, Redhill County Hospital, Middlesex;* and L. Fatti, F. R. C. S., *Thoracic Surgeon, Hillingdon County Hospital and Harefield County Hospital, Middlesex.* 2d edition. 720 pages, illustrated. Geoffrey Cumberlege, Oxford University Press, New York, N. Y., publishers, 1948. Price $18.50.

This comprehensive treatise reflects the opinions of the pathologist, medical man, and surgeon. It deals extensively with pathogenesis, diagnosis, and general management, and less with matters of prognosis and epidemiology. The exhaustiveness of the discussion and bibliography, the clinical and experimental pathology cited, the descriptions and illustrations of specialized techniques, place this book beyond the sphere of reference literature for the medical student, general practitioner, and surgeon.

The first part deals mainly with the pathogenesis of tuberculosis, both primary and "post-primary." The importance of the primary lesion in recurrence of active disease is stressed, as is the relation of pulmonary and extrapulmonary forms.

The various forms of pulmonary tuberculosis observed are well documented by case histories and reproductions of roentgenograms.

The following conditions are discussed in the differential diagnosis (and concurrence with tuberculosis): pneumonitis, bronchiectasis, chronic bronchitis, lung abscess, pneumoconiosis, cancer, and sarcoidosis.

Under treatment, the value of streptomycin is assessed, collapse therapy is most extensively discussed, although the medical regimes in common use are not overlooked. Pathologic physiology is discussed in connection with cavities, noncavitary lesions, and atelectasis. Artificial pneumothorax, intrapleural pneumonolysis, phreniclasia, artificial pneumoperitoneum, and thoracoplasty are evaluated. Cavity drainage and extirpative measures are touched upon. The chapter on choice of procedures is of value.

From the public-health standpoint the measures for prevention and control include: segregation of active cases, pure milk supplies for children, BCG vac-

cination for children and adults who may be exposed to active cases, and periodic tuberculin testing and radiographic studies are discussed.

The appendices include the classifications used by the Ministry of Health in Great Britain, and the National Tuberculosis Association in the United States.—*Lt. (jg) F. W. Meyer, Jr., (MC) U. S. N.*

GERIATRIC MEDICINE, The Care of the Aging and the Aged. Edited by Edward J. Stieglitz, M. S., M. D., F. A. C. P., *Attending Internist, Suburban Hospital, Bethesda, Md. (Chairman, Staff, 1945–47); Doctor's Hospital, Washington, D. C.; Attending Internist (Geriatrics), Chestnut Lodge, Rockville, Md.; Consulting Internist, Washington Home for Incurables; Associate, Washington School of Psychiatry; Special Lecturer, Institute of Industrial Medicine, New York University, Bellevue Postgraduate Medical School, New York City; Formerly Associate Clinical Professor of Medicine, Rush Medical College, The University of Chicago.* 2d edition. 773 pages, illustrated. W. B. Saunders Co., Philadelphia, Pa., publishers, 1949. Price $12.

In the second edition of this standard reference book, Dr. Stieglitz has presented the problems of caring for the aging and aged. He has added and integrated the talents of 46 distinguished collaborators, each an authority in his own field, thereby providing a more comprehensive discussion of the biology of aging.

The achievements of preventive medicine in controlling infectious diseases and the benefits of improved infant care have conferred a longer life expectancy upon our population. The problems of this "aging population" are dealt with in essay style, system by system, and disease by disease.

The belief that arteriosclerosis is a natural accompaniment of aging is no longer tenable in light of present knowledge. This problem is discussed clearly by Dr. Irving S. Wright.

Other diseases of stress and degeneration are considered with the suggestion implicit that preventive medicine might well prepare and redirect its energies toward problems in the field of geriatrics, long neglected and long considered to be irreversible and irreparable.

As with any medical work, there are unwritten chapters, for progress in the field of endocrinology has outstripped the pace of the printer. Other sources must be sought for a view of the forward-moving scene involving ACTH, cortisone, the Selye hypotheses, and other pertinent correlations.

To all readers in search of an introduction to the very important medical problems incident to the care of the aging and the aged, this book is a rich storehouse of information, presented in a clear and concise manner.—*Commander G. L. Calvy, (MC) U. S. N.*

REFRACTION OF THE EYE, by Alfred Cowan, M. D., *Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Active Consulting Ophthalmologist, Philadelphia General Hospital; Consulting Ophthalmologist, Council for the Blind and Supervising Ophthalmologist of the Department of Public Assistance, Commonwealth of Pennsylvania.* 3d edition, thoroughly revised, with 187 illustrations and 3 colored plates. Lea & Febiger, Philadelphia, Pa., publishers, 1948. Price $5.50.

This work accomplishes the author's purpose in that it is "a book on clinical refraction employing the theory of ophthalmic optics in such a way that clinical aspects would emerge logically and in orderly sequence from their bases of scientific facts."

The illustrations are excellent, especially the three colored plates. All these help in the logical sequence of proof presented by the author for the laws of refraction and reflection.

The early chapters deal with light and its propagation; laws of reflection and laws of refraction, with mathematical proof for a pencil of light as it is affected by reflecting surfaces, prisms, thin and thick lenses of various forms—including

optical lenses, as well as the eye contents (cornea, aqueous, pupil formed by the iris, lens, vitreous, and retina). A recapitulation of laws of optics is presented summarizing each chapter. The chapter on ametropia is excellent in its presentation of theory, fact, and explanation. Methods of refraction are well explained, giving procedure and description of equipment necessary in performing the various phases of different methods, both objective and subjective. The prescribing of lenses for measuring visual acuity is delineated in logical steps with a discussion of the various special types of lenses, contact glasses, and telescopic spectacles.

A large bibliography with a complete index closes this well-prepared book. It will be a temporary closing only, for the student or ophthalmologist will find his memory refreshed with precisely illustrated facts. He will use it later as a reference for proof in refraction as its affects the human eye.

This third edition of Cowan's Refraction of the Eye should replace older volumes, especially in our teaching centers because many concepts of clinical aspects as well as scientific data have changed since the last edition. Present concepts as found herein are now used in teaching at the American Academy of Ophthalmology and Otolaryngology as well as in home study courses covering the field of ophthalmology. This newer knowledge is necessary in order to pass the American Board examinations.—*Capt. C. B. Johnson, (MC) U. S. N.*

PEDIATRIC ANESTHESIA, by M. Digby Leigh, M. D., *Director of Anesthesia, Vancouver Hospital, Vancouver, Canada; Diplomate of the American Board of Anesthesiology; Formerly Director of Anesthesia, Children's Memorial Hospital, Montreal, Canada; Formerly Assistant Professor of Anesthesia, McGill University, Montreal, Canada;* and M. Kathleen Belton, M. D., *Supervisor of Pediatric Anesthesia, Vancouver General Hospital, Vancouver, Canada; Formerly Assistant Director of Anesthesia, Children's Memorial Hospital, Montreal, Canada; Formerly Demonstrator in Anesthesia, McGill University, Montreal, Canada.* 240 pages, illustrated. The Macmillan Co., New York, N. Y., publishers, 1948. Price $5.50.

Doctors Leigh and Belton have drawn upon their extensive clinical experience to write a book which is well organized, easily read, and a "must" on the library list of every anesthesiologist.

It is only in the past few years that we have to come to recognize and understand more fully the differences between adult and child physiology, differences which are of the utmost importance to the anesthetist. The greater metabolism of the child makes him less able to tolerate extremes of anesthesia or oxygen lack. The authors point out these differences and their significance so far as margin of safety is concerned, particularly in their discussion of respiration and circulation.

The proper psychological approach assumes greater significance when dealing with children, and the preoperative visit and medication are given considerable attention in this book. Optimal drug dosage for adequate premedication is presented.

All the various technics of anesthesia are discussed, and there is a very comprehensive chapter on the choice of anesthetic agent and technic. Inhalation anesthesia is emphasized, particular reference being made to the use of Ayre's T tube and a valve which allows inhalation of atmospheric air. Indications for intubation and the disadvantages of this technic are given. More might have been said about the use of curare in pediatric anesthesia.

Special chapters are devoted to complications, postoperative care, and oxygen and fluid therapy.

This book deserves unqualified recommendation because of its excellent coverage of a specific field within that of anesthesiology.—*Lt. (jg) B. H. Pender (MC) U. S. N.*

DENTISTRY IN PUBLIC HEALTH, edited by Walter J. Pelton, B. S., D. D. S., M. S. P. H., *Dental Surgeon, U. S. Public Health Service, Colorado,* and Jacob M. Wisan, D. D. S., M. S. P. H., *Director, Joseph Samuels Dental Clinic, Rhode Island State Hospital, for the Dental Health Section of the American Public Health Association.* 363 pages; illustrated with 64 figures. The W. B. Saunders Co., Philadelphia, Pa., publishers, 1949. Price $5.50.

Forces generated by the pressure of accumulated knowledge shape the course of events in all fields of endeavor. It is in response to such forces in the field of public health that Pelton and Wisan have contributed a most interesting and highly significant composite text.

This book constitutes a compilation of material derived from authoritative sources, all of which is relevant to dentistry's current status in the sphere of public health. It is composed of 17 chapters covering 352 pages, with 64 figures, and is well indexed for ready reference. Each chapter has a comprehensive bibliography which may be used by readers to obtain detailed information with regard to the subject matter.

The introductory chapter by Louis S. Reed, Ph. D., sets the stage by the portrayal of sociologic trends and developments affecting all health services, thus providing the necessary background by a description of the medical health plans which have been sponsored and/or adopted by medical groups and governmental agencies. Logical continuity then progresses to a consideration of "Dentistry in the Public Health Movement," a chapter presented by William R. Davis, D. D. S.; Melvin L. Dollar, B. S., and Hugo Kulstad, D. D. S., deal with the "Economic Aspects of the Dental Health Problem" as related to dental needs and the cost and demand for dental care. Mathematical principles quantitatively applied to biologic materials, dental biometrics, constitute a masterful chapter written by Marguerite Hall, Ph. D. This material will have special appeal to research workers and dentists who are interested in a critical analysis of problems in the dental health field.

John W. Knutson, D. D. S., Dr. P. H., gives a clear word picture of the methodology involved in making statistical surveys and in evaluating various types of dental programs. Nina Simmonds, Sc. D., a prominent nutritionist, narrates the story of nutrition, beginning with a brief historical background which leads to the Present Concept of Food as a Factor in Dental Disease; included in this narrative is a tabulation of 7 groups of foods suitable for checking the adequacy of patients' diets. Philip Jay, D. D. S., M. S., Sc. D., depicts the modality of clinical laboratory tests for determination of caries activity.

Fluorine, scientifically considered from the viewpoints of early and recent research, is exceptionally well-presented by two prominent investigators and writers in the field of public health, H. Trendley Dean, D. D. S., and Francis A. Arnold, Jr., D. D. S. The former concerns himself with epidemiological characteristics of fluorosis, while the latter deals with fluorine in its systemic, oral, environmental, experimental, and control aspects.

Philip Blackerby, Jr., D. D. S., M. S. P. H., reports the development, current status, and trends of treatment in public health dentistry on the National, State, and local levels. The definition, need, and methodology of dental health education is succinctly recounted by Dorothy B. Nyswander, Ph. D.

A general review of administrative problems in dental health programs and the manner in which dentistry fits into the operation of health departments is sketched by Walter J. Pelton, D. D. S., M. S. P. H. This review of general considerations is supplemented and amplified by delineation of local dental health programs aptly described by Allen O. Gruebbel, D. D. S., M. P. H.; dental programs in urban communities by Harry Strusser, D. D. S., M. S. P. H.; and State dental programs by Frank C. Cady, D. D. S., M. P. H. A concluding chap-

ter by Harold Hillenbrand, D. D. S., briefly describes the principal dental professional Associations and Foundations.

America today is undoubtedly more sociologically inclined than at any previous time in its history. Transitory influences characteristic of postwar eras, capable of profoundly affecting the health of the Nation and the status of the health professions should be critically evaluated in the light of present knowledge. Members of the health professions should familiarize themselves with the contents of this book in order to have an intelligent concept of current influences in order to supply the leadership necessary to serve the best interests of their country and their profession.—*Capt. M. M. Maxwell, (DC) U. S. N.*

RADIOLOGIC EXPLORATION OF THE BRONCHUS, by S. di Rienzo, M. D., *Assistant Professor of Radiology and Physiotherapy, Chief of the Radiology Department of the Institute of Cancer, The University of Córdoba, Argentina.* Translated by Tomas A. Hughes, M. D., with a foreword by Richard H. Overholt, M. D. 332 pages, illustrated. Charles C Thomas, Springfield, Ill., publisher, 1949. Price $10.75.

This book should be of value to the radiologist, physician, and surgeon, because it stresses the assistance of good bronchography in both the diagnosis and precise localization of pathologic lung changes. The fact that the book contains numerous typographical errors and that some of the terminology is strange to the North American student should not detract from its over-all value. In the discussion of both normal and pathologic conditions, the dynamics of the respiratory tree as revealed by the bronchographic procedure are continually emphasized. The book is profusely illustrated.

BOOKS RECEIVED

Receipt of the following books is acknowledged. As far as practicable, these will be reviewed at a later date.

JORDAN-BURROWS TEXTBOOK OF BACTERIOLOGY, by William Burrows, Ph. D., *Professor of Bacteriology, Department of Bacteriology and Parasitology, the University of Chicago.* With the collaboration of Francis Byron Gordon, Ph. D., M. D., *Biological Department, Chemical Corps, Camp Detrick, Maryland; formerly Professor of Bacteriology, Department of Bacteriology and Parasitology, the University of Chicago;* Richard Janvier Porter, Ph. D., *Associate Professor of Parasitology, School of Public Health, the University of Michigan;* and James William Moulder, Ph. D., *Assistant Professor of Biochemistry, Department of Bacteriology and Parasitology, the University of Chicago.* 15th edition. 981 pages; illustrated with 264 figures. W. B. Saunders Co., Philadelphia, Pa., publishers, 1949. Price $9.

THE VERTEBRATE BODY, by Alfred Sherwood Romer, *Alexander Agassiz Professor of Zoology, and Director, Museum of Comparative Zoology, Harvard University.* 643 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., publishers, 1949. Price $5.50.

HISTOPATHOLOGY OF THE SKIN, by Walter F. Lever, M. D., *Instructor in Dermatology, Harvard Medical School; Assistant Dermatologist, Massachusetts General Hospital; Associate in Dermatology, Peter Bent Brigham Hospital; Consulting Dermatologist, Massachusetts Eye and Ear Infirmary.* 449 pages; 221 illustrations, including 8 subjects in color on 4 pages. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $10.

PHARMACEUTICAL COMPOUNDING AND DISPENSING, Editor in Chief Rufus A. Lyman, M. D., *Dean, College of Pharmacy, University of Arizona;* Technical Editor George Urdang, Ph. G., D. Sc. Nat., *Director, American Institute of History of Pharmacy; Professor of the History of Pharmacy, University of Wisconsin,* with 6 advisory editors and 11 contributors. 13th revision. 321 pages; illustrated. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $6.50.

HUMAN PATHOLOGY, by Howard T. Karsner, M. D., LL. D., *former Professor of Pathology, Western Reserve University; Medical Research Advisor to the Bureau of Medicine and Surgery, United States Navy.* 7th edition. 927 pages; 562 illustrations in

black and white and 22 subjects in color on 14 plates. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $12.

THE DIAGNOSIS OF PANCREATIC DISEASE, by Louis Bauman, M. D., *formerly Assistant Professor of Clinical Medicine, Columbia University, and Assistant Visiting Physician to the Presbyterian Hospital, New York.* With a foreword by Allen O. Whipple, M. D. 74 pages. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $5.

THE PHYSICIAN'S BUSINESS, Practical and Economic Aspects of Medicine, by George D. Wolf, M. D., *Assistant Clinical Professor, Otolaryngology, New York Medical College; Fellow, New York Academy of Medicine; Fellow, American Medical Association.* Foreword by Harold Rypins, A. B., M. D., F. A. C. P. 3d edition. 563 pages; 96 illustrations. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $10.

FRACTURES, by Paul B. Magnuson, M. D., F. A. C. S., *Professor of Bone and Joint Surgery and Chairman of the Department, Northwestern University Medical School; Attending Surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago;* and James K. Stack, A. B., M. D., F. A. C. S., *Assistant Professor of Bone and Joint Surgery, Northwestern University Medical School; Attending Surgeon, Passavant Memorial Hospital and Cook County Hospital, Chicago.* 5th edition. 537 pages; 323 illustrations. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $7.

INORGANIC CHEMISTRY IN PHARMACY, by Lloyd M. Parks, Ph. D., *Professor of Pharmaceutical Chemistry, University of Wisconsin;* Paul J. Jannke, Ph. D., *Associate Professor of Pharmaceutical Chemistry, University of Connecticut,* and Loyd E. Harris, Ph. D., *Professor of Pharmacy, Ohio State University,* with a chapter on Isotopes by John E. Christian, Ph. D., *Co-ordinator of Bio-Nucleonic Research, School of Pharmacy, Purdue University.* 298 pages. J. B. Lippincott Co., Philadelphia, Pa., publishers, 1949. Price $6.

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